IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Tommy Ekstrom	Art Unit	: 1627
Serial No.	: 10/665,240	Examiner	: Kendra D. Carter
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Title : NEW USE

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BRIEF ON APPEAL

Appellant is appealing the final rejection of claims 13-29, 34, 36, 42-50, 52-55, and 57-66 in the final Office Action dated August 20, 2010. A Notice of Appeal was filed and received by the U.S. Patent and Trademark Office on January 10, 2011, along with Appellant's Pre-Appeal Brief Request for Review. The Panel Decision from Pre-Appeal Brief Review was mailed February 7, 2011.

(i) Real Party in Interest

The Real Party in Interest is AstraZeneca AB, the assignee of record, which is a subsidiary of AstraZeneca PLC.

(ii) Related Appeals and Interferences

The Board of Patent Appeals and Interferences (the Board) issued a decision in Appeal 2007-1154 in a related case, U.S. Serial No. 09/367,950, on August 28, 2007. The present application is a continuation of that related case. A copy of the Board's decision in Appeal 2007-1154 is included in the Related Proceedings Appendix, Appendix (x), attached hereto. There are no other prior or pending related appeals, judicial proceedings, or interferences.

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(iii) Status of Claims

Claims 1-12, 30-33, 35, 37-41, 51, 56, 67, and 68 are canceled.

Claims 13-29, 34, 36, 42-50, 52-55, and 57-66 are rejected and under appeal.

(iv) Status of Amendments

Appellant filed a Supplemental Amendment on July 29, 2011, canceling claims 51, 56, 67, and 68. To Appellant's knowledge, that amendment had not been acted upon as of the date this Brief was filed. No other amendments have been filed subsequent to the August 20, 2010, mailing date of the Final Office Action, and none are being submitted herewith.

The attached Claims Appendix, Appendix (viii), shows the status of Claims 51, 56, 67 and 68 as canceled.

(v) Summary of Claimed Subject Matter

The claims are directed to methods of treating asthma in a patient. Claims 13, 36, 42, 49, and 50 are the independent claims. As dependent claims 16, 19, and 57-66 are separately discussed, they also are summarized here.

Independent claim 13 is directed to methods of treating asthma in a patient, the methods comprising administering an effective amount of a composition including, in admixture, (a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient that is budesonide. The patient is administered both (i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses on an irregular basis, wherein the one or more additional doses are administered as-needed, as determined by the patient. Support for claim 13 can be found in the specification, *e.g.*, at page 2, lines 18-28; page 3, lines 11-16; page 4, lines 2-23; and page 8, lines 24-29.

Dependent claim 16 depends from claim 13 and further specifies that the first active ingredient is the R,R enantiomer of formoterol or a pharmaceutically acceptable salt or solvate of

said enantiomer or a solvate of such a salt. Support for claim 16 can be found in the specification, e.g., at page 5, line 6.

Dependent claim 19 depends from claim 13 and further specifies that the second active ingredient is the 22R epimer of budesonide. Support for claim 19 can be found in the specification, e.g., at page 5, lines 16-17.

Independent claim 36 is directed to methods of treating asthma in a patient, the methods comprising administering an effective amount of a composition including, in admixture, (a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient that is budesonide. The patient is administered both (i) a maintenance dose of the composition twice per day on a regular basis, and (ii) one or more additional doses on an irregular basis, wherein the one or more additional doses are administered when the patient expects to encounter an asthma inducing condition. Support for claim 36 can be found in the specification, *e.g.*, at page 2, line 18, through page 3, line 19; page 4, lines 2-23; and page 8, lines 24-29.

Independent claim 42 is directed to methods of treating asthma in a patient, the methods comprising administering an effective amount of a composition including, in admixture, (a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient that is budesonide. The patient is administered both (i) a maintenance dose of the composition twice per day on a regular basis, and (ii) one or more additional doses that are administered when the patient experiences an acute asthma attack. Support for claim 42 can be found in the specification, *e.g.*, at page 2, line 18, through page 3, line 30; page 4, lines 2-23; and page 8, lines 24-29.

Independent claim 49 is directed to methods of treating asthma in a patient, the methods comprising administering an effective amount of a composition including, in admixture, (a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient that is budesonide. The patient is

administered both (i) a maintenance dose of the composition twice per day on a regular basis, and (ii) one or more additional doses on an irregular basis, the additional doses being administered when needed for symptom relief. Support for claim 49 can be found in the specification, *e.g.*, at page 2, line 18, through page 4, line 23; and page 8, lines 24-29.

Independent claim 50 is directed to methods of treating asthma in a patient, the methods comprising administering an effective amount of a composition including, in admixture, (a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt, and (b) a second active ingredient that is budesonide. The patient is administered both (i) a maintenance dose of the composition on a regular basis as determined by the patient's physician, and (ii) one or more additional doses on an irregular basis, the one or more additional doses being administered when the patient determines the additional dose or doses are needed for symptom relief or when the patient expects to encounter an asthma inducing condition. Support for claim 50 can be found in the specification, *e.g.*, at page 1, line 29, to page 2, line 3; page 2, line 18, to page 4, line 23; and page 8, lines 24-29.

Dependent claim 57 depends from claim 13, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient. Support for claim 57 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 58 depends from claim 13, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient. Support for claim 58 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 59 depends from claim 36, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient. Support for claim 59 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 60 depends from claim 36, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient. Support for claim 60 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 61 depends from claim 42, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient. Support for claim 61 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 62 depends from claim 42, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient. Support for claim 62 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 63 depends from claim 49, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient. Support for claim 63 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 64 depends from claim 49, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient. Support for claim 64 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 65 depends from claim 50, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient. Support for claim 65 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

Dependent claim 66 depends from claim 50, further specifying that the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient. Support for claim 66 can be found in the specification, e.g., at page 8, line 28; and page 9, lines 5-6.

(vi) Grounds of Rejection to be Reviewed on Appeal

A. Claims 13-15, 17, 18, 20-29, 34, 36, 42-50, and 52-55 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (WO 93/11773; copy enclosed for the Board's convenience as Exhibit 11 in the Evidence Appendix).

B. Claims 16 and 19 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* in view of Aberg *et al.* (U.S. Patent No. 5,795,564; copy enclosed as Exhibit 12 in the Evidence Appendix) and Ryrfeldt *et al.* (*Biochem Pharmacol.* 38:17-22, 1989; copy enclosed as Exhibit 13 in the Evidence Appendix).

C. Claims 57-66 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* in view of Trofast (U.S. Patent 5,983,956; copy enclosed as Exhibit 14 in the Evidence Appendix).

D. Claims 13-15, 17, 19, 20, 22-25, 34, 36, 42, 53 and 57-66 are provisionally rejected for alleged nonstatutory obviousness-type double patenting over claims 13-15, 17, 19, 20, 22-25, 30-36, 38, and 42 of co-owned U.S. Application No. 09/367,950.

(vii) Argument

A. Rejection of claims 13-15, 17, 18, 20-29, 34, 36, 42-50, and 52-55 for obviousness over Carling *et al.*

Claims 13-15, 17, 18, 20-29, 34, 36, 42-50, and 52-55 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Carling *et al.* (WO 93/11773; hereinafter "Carling *et al.*").

As the U.S. Supreme Court reconfirmed in *KSR International Co. v. Teleflex Inc. et al.*, 127 S.Ct 1727, 1734 (2007), analysis and determination of obviousness under § 103(a) requires determination of the scope and content of the prior art, differences between the prior art and the

claims in issue, and the level of ordinary skill in the pertinent art. *Graham v. John Deere*, 383 U.S. 1, 17 (1966). See also MPEP 2141(II). When applying § 103(a), the examiner must consider the claimed invention as a whole; must consider the prior art as a whole; and must view the reference without the benefit of impermissible hindsight vision afforded by the claimed invention. *Graham,* 383 U.S. at 36; see also MPEP 2141.02(I). Any rejection of a claim for obviousness must establish that there would have been a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR*, 127 S.Ct. at 1741. In addition, the examiner's *prima facie* case must include a finding that one of ordinary skill in the art at the time the invention was made would have reasonably expected the claimed invention to work. *See, Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.,* 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). It is well established that a teaching-away in the art can be highly probative of nonobviousness (*KSR*, 127 S.Ct at 721, citing *United States v. Adams et al.,* 383 U.S. 39; 86 S.Ct. 708 (1966). Such objective considerations as surprising results (*United States v. Adams et al.,* 383 U.S. at 51-52; *In re Soni,* 54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995)), long felt but unsolved need (*Dow Chem. Co. v. American Cyanamid Co.*, 816 F.2d 617, 622, 2 USPQ2d 1350, 1355 (Fed. Cir. 1987), and skepticism of experts (*United States v. Adams*, 383 U.S. at 52) are also relevant to the obviousness inquiry. "Proceeding contrary to the accepted wisdom. . . is "strong evidence of unobviousness.'" *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). When technical experts praise the patented technology, that constitutes evidence supporting the nonobviousness of the patent. *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559 (Fed. Cir. 1996), *remanded*, 520 U.S. 111 (1997), *aff'd in part, rev'd in part, vacated in part & remanded*, 140 F.3d 1499 (Fed. Cir. 1998), *petition for reh'g denied & suggestion for reh'g in banc declined*, 145 F.3d 1472 (Fed. Cir. 1998).

All of the present claims are drawn to treating asthma in a patient by a method comprising administering a composition comprising formoterol (or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt) and budesonide. Formoterol is a β_2-agonist, a bronchodilator that helps reduce the bronchoconstriction-induced symptoms of asthma. (See, e.g., Carling *et al.*, page 2, lines 14-27.) In contrast, budesonide is not a bronchodilator. It is a steroid: a glucocorticosteroid, to be precise. Although steroids inherently carry a risk of

significant systemic side effects, and for that reason their use by patients is normally tightly controlled by the patients' physicians, budesonide has been successfully used for many years in the long-term "maintenance" treatment of chronic asthma because it helps reduce the chronic inflammation in asthma that may lead to mucosal damage and structural changes leading to irreversible narrowing of the airways and fibrosis of the lung tissue. (Carling *et al.*, page 1, lines 27-33.) The art understood that inhaled steroids do not give immediate symptom relief (Carling *et al.*, page 2, lines 5-7) and do not relieve an acute asthma attack. This is an important point, because the rejection appears to be based on an unstated assumption that one of ordinary skill in the art at the time of the invention would have believed it obvious to utilize a composition containing budesonide to relieve the immediate symptoms of asthma. As the evidence discussed below will show, this assumption is not valid.

While all of the independent claims require administration of a composition comprising formoterol (or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt) and budesonide, the various claims differ in the details of the administration, as follows.

Independent claims 13, 36, 49, and 50 (and the claims that depend from them) all require that the patient is administered both (i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses on an irregular basis. These four claims go on to say that the one or more additional doses are administered as-needed, as determined by the patient (claim 13); or when the patient expects to encounter an asthma inducing condition (claim 36); or when needed for symptom relief (claim 49); or when the patient determines the additional dose or doses are needed for symptom relief or when the patient expects to encounter an asthma inducing condition (claim 50). Claim 50 also includes a further requirement that the twice-per-day maintenance dose be administered on a regular basis as determined by the patient's physician.

Independent claim 42 requires that the patient be administered both (i) a maintenance dose of the composition twice per day on a regular basis, and (ii) one or more additional doses when the patient experiences an acute asthma attack.

It can be seen from the above that each of the claims includes a limitation requiring that, in addition to any maintenance dosing specified in the claim, one or more doses of the

formoterol/budesonide composition are administered "as needed, as determined by the patient" or "when the patient expects to encounter an asthma inducing condition" or "when the patient experiences an acute asthma attack" or "when needed for symptom relief" or "when the patient determines the one or more doses are needed for symptom relief." These one or more doses are specified as being in addition to the regular "maintenance dose" of the composition that is given twice per day or as determined by the patient's physician. Although a regular maintenance regimen using the formoterol/budesonide composition was known in the art (see Carling *et al.*), arriving at the presently claimed methods required a striking insight by Appellant: that allowing the patient to take additional doses of a combination budesonide/formoterol composition (in addition to the fixed twice-per-day maintenance dose that was known in the art), and leaving it to the patient's discretion to decide when and how many of those additional doses to take according to the patient's determination of need, would greatly reduce the number of severe asthma attacks (exacerbations) suffered by the patient; and that this could be done without incurring in practice a substantial risk of overdose of budesonide, a potent glucocorticosteroid. In addition, Appellant found that treatment in accordance with the claimed invention would improve symptom control and lung function, compared to treatment as taught in the art. These insights were nowhere in the prior art, and in fact represented a radical departure from how patients were instructed to take budesonide-containing compositions prior to 1998, the priority date of the present application.

Carling *et al.* is cited as rendering the claimed methods obvious. Carling *et al.* discloses treatment of asthma by regular, twice daily inhalation of a combination of formoterol and budesonide from a single inhaler. According to Carling *et al.* at page 4, lines 19-21, "The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma." (Emphasis added.) Similarly, page 6, lines 22-29, says, "The intended dose regimen is a twice daily administration…." Such a set, twice-daily regimen has long been, and still is today, a standard asthma treatment protocol for administering anti-inflammatory glucocorticosteroids such as budesonide. Commonly termed "maintenance therapy," it is intended to reduce over the long term the underlying chronic inflammation that, if uncontrolled, can contribute to the overall disease. Typically the asthma patient will also be prescribed a second inhaler containing a short-acting bronchodilator such as terbutaline for emergency use whenever needed to stop an imminent or ongoing attack that

occurs despite the glucocorticosteroid maintenance therapy regimen. Use of that short-acting bronchodilator is left to the discretion of the patient. In contrast, use of budesonide or other powerful glucocorticosteroids is not—or at least wasn't until the present invention. As will be clear from evidence discussed in detail below, patients who, prior to the present invention, were prescribed a budesonide-containing inhaler were warned not to take any more (or any fewer) doses from their budesonide inhaler than the two fixed doses per day prescribed by the physician for maintenance therapy. While the patients were permitted to decide on their own when and if to use their short-acting bronchodilator inhalers for emergency relief, they were never permitted to use their budesonide-containing inhalers that way. This reflects both what was perceived to be the relatively slow-acting nature of glucocorticosteroids, rendering them mostly useless in an acute attack, and the danger of systemic side effects from overdosing on glucocorticosteroids in general. While the physician had the discretion to adjust the size of the two fixed daily doses of glucocorticosteroid according to factors such as the age and weight of the patient or the severity of the patient's illness, such adjustments were solely at the discretion of the physician, and were adjustments to the regular (i.e. twice daily) maintenance dosing. The patient would not make that decision, and the number of administrations of budesonide or other glucocorticosteroid would generally remain at twice per day even if the prescribed fixed dosage per administration were changed by the physician. Evidence supporting these assertions, including statements derived from various inhaler product inserts, is discussed below.

The final Office Action dated August 20, 2010 (the "Final Office Action") cites Carling *et al.* for its teaching that a composition comprising both formoterol and budesonide can be used to treat asthma, alleging at page 7 that "The amounts of active agents per dose of inhalation are disclosed on pages 7-9 [of Carling *et al.*], which calculate up to 8 inhalation per day without going over the maximum daily dosage." Carling *et al.* says nothing about "up to 8 inhalation per day." As best as Appellant can decipher it, the Examiner's phrase "up to 8 inhalation per day" is meant to refer to some of Carling *et al.*'s examples of inhalers described on pages 7-9 as delivering 12 μg of formoterol and either 100 or 200 μg budesonide, combined with Carling *et al.*'s teaching on page 6, lines 24-26, that a "suitable daily dose" of formoterol is 6 to 100 μg and a "suitable daily dose" of budesonide is 50 to 4800 μg. Thus, in theory one could inhale eight "inhalations" or "puffs" from an inhaler that delivers a combination of 12 μg

formoterol and 100 or 200 μg budesonide per puff without exceeding what Carling *et al.* teaches is the upper end of the range of a suitable daily dose of formoterol (100 μg) and the upper end of the range of a suitable daily dose of budesonide (4800 μg). The reference itself actually says nothing about the number of inhalations per administration, rather only that those inhalations should be grouped into just two administrations per day ("the intended dose regimen is a twice daily administration" (page 6, lines 22-23)) and should deliver a total daily dose within the recommended ranges. Each of the two administrations per day intended by Carling *et al.* could, in theory, involve a single "puff", or two or more "puffs," to achieve the fixed daily dosage prescribed by the physician using whatever inhaler is commercially available. The mere fact that a particular inhaler delivers a dose that is less than half of a prescribed daily dose does not mean that the prescribed daily dose should be spread out into more than two administrations per day. In fact, doing so would be in contravention of Carling *et al.*'s explicit teachings that the intended dose regimen is twice daily. The Examiner's interpretation to the contrary, which is central to her obviousness theory, is therefore without basis in the reference.

The Examiner recognizes that Carling *et al.* does not teach that the patient should be instructed to inhale the composition on an "on demand" or "as needed" basis, as required by the claims. As acknowledged in the final Office Action at page 7,

> Carling et al. does not specifically teach one or more additional doses on an irregular, as-needed basis for rescue purposes, as determined by the patient (claim 13), based on the patient's symptoms, when (1) the patient experiences an increase in asthma symptoms as set forth in applicant's claim 13; or (2) when the patient is expecting to encounter an asthma inducing condition… (applicant's claims 34, 36, 50 and 51). Carling et al. does not teach to inhale additional doses as needed to improve control and provide acute relief (applicant's claim 42).

Nevertheless, the Examiner concludes that, despite this acknowledged lack of teaching in the reference, use of the composition in the dosage regimens required by the present claims would have been obvious:

> To one of ordinary skill in the art, it would have been obvious to combine the method of Carling et al. and administering the method on an irregular, as-needed basis for rescue purposes, as determined by the patient in any of the circumstances detailed in claims 13, 34, 36, 42 and 49-51 because Carling et al. teaches that the dosages strongly depends on the severity of disease, whether

> mild, moderate, or [severe] asthma (see pg 6, lines 27-29), and the suitable daily dosage is up to 8 inhalation (see page 7-9).
>
> The motivation to combine the methods and compositions of Carling et al. and instructing the patient to inhale, on demand in any of the circumstances detailed in claims 13, 34, 36, 42 and 49-51 because Carling et al. teaches that the dosages strongly depends on the severity of disease and to achieve maximum benefit of daily dosage recommended. It is noted by Carling et al. that the combination of formoterol with budesonide is well known to be beneficial for the treatment of asthma (see page 4, lines 4-21). Moreover, if the patient is experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, the patient can still safely inhale an additional 6 inhalations without going over the maximum suitable daily dosage. In general, Carling et al. teaches therapeutic relief from asthmatic attack. The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is for reasonable expectation of successfully achieving maximum benefit in the treatment of any level of the asthma condition, including an increase in asthma symptoms, acute asthmatic condition, maintenance treatment, and common asthma triggers. Additionally, due to the urgency of therapy during an asthma attack, a patient would obviously seek relief with the medication without consulting with the physician, in knowing the safe daily dosage range of each medication. Final Office Action at pages 8-9; non-standard English in the original.

In order to arrive at this conclusion, the Examiner had to make two assumptions about the Carling *et al.* reference: *first*, that Carling *et al.* can be read as teaching that the maximum daily dose of the active ingredients can be spread out in as many as eight discrete administrations over the course of the day, and *second*, that Carling *et al.* suggests that it is up to the patient to determine how many of those eight administrations to take on any given day, based on the patient's self-assessment of "severity of disease." The lack of basis for the *first* assumption is discussed above. The *second* assumption is even more far-fetched than the first. It seems to derive from the sentence at page 6, lines 27, of Carling *et al.* that "[the] particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)." This sentence of course would have been understood by one of ordinary skill in the art as intended to mean that the physician will determine a fixed dose that depends on the patient's age, weight, and severity of disease, and not that the patient should make these determinations for himself or herself. In fact, it seems fairly ridiculous to have to explain that point at all. The only dosing regimen disclosed in Carling *et al.* is regular, twice daily dosing.

The twice-daily dose regimen called for by Carling *et al.* is a fixed dosage prescribed by the physician for the patient to inhale on a regular basis two times per day, every day, no more and no less, consistent with what was known in the art about administration of any budesonide-containing composition for treatment or prevention of asthma symptoms. The amount inhaled at each administration can be varied only by a change in the prescription by the physician, again consistent with what was known in the art about administration of any budesonide-containing composition in the asthma context. (All of this is amply proven by several documents of record in the case, the details of which are discussed below.)

Further, to arrive at the conclusion that the claims are obvious, the Examiner had to intermingle those two assumptions about how to interpret Carling *et al.* with a third assumption that is not based on Carling *et al.* nor any other cited art: that one of ordinary skill in the art would have ignored the understanding in the art that glucocorticosteroids such as budesonide (a) are slow-acting, (b) are not bronchodilators, (c) do not provide immediate relief from acute asthma attacks, and (d) pose a risk of dangerous side effects from overdosing, and would nevertheless have selected Carling et al.'s composition containing budesonide and formoterol, rather than a standard relief inhaler containing a short-acting bronchodilator, for use to relieve an urgent asthma attack. There is no basis in Carling *et al.,* or anywhere else in the art, for the Examiner's assertion that a patient would "obviously seek relief" with the budesonide/formoterol combination during an asthma attack. Though Carling *et al.* does use the term "rescue medicine" at page 4, line 8, the context of this phrase shows that Carling *et al.* was simply describing the rapid onset of action of formoterol (a long-acting β2 agonist) when used in a twice-per-day maintenance regimen, compared to the slower onset of other long-acting β-agonists such as salmeterol. There is no suggestion in Carling *et al.* that the budesonide/ formoterol combination should be taken more than twice per day, and certainly no suggestion that it be taken "as needed" or for relief during an acute asthma attack. In fact, the sentence at the end of the paragraph in Carling *et al.* that mentions "rescue medicine" clearly states how the budesonide/formoterol combination should be used: "**The combination according to the present invention permits a twice daily dosing regime as a basic treatment of asthma, including nocturnal asthma.**" (emphasis added) One of ordinary skill in the art would understand Carling *et al.* to have intended that the combination be administered in precisely the daily amount prescribed by the

physician, no more and no less, and that the daily amount should be divided into precisely two administrations each day—presumably one in the morning and one in the evening. For emergency relief of an asthma attack, one of ordinary skill in the art knew to use short-acting β2 agonist bronchodilators such as terbutaline, and not long-acting β agonists such as formoterol or medications containing budesonide or other glucocorticosteroids.

In contrast to the utter lack of evidence of record to support the Examiner's position, Appellants have provided several lines of evidence (discussed below) to show that her position is unwarranted.

As evidence that one of ordinary skill in the art of asthma therapy would have agreed with Appellant's interpretation of Carling *et al.*, and not with the Examiner's interpretation, Appellant refers the Board to certain exhibits submitted with Appellant's Amendment dated July 27, 2007. These exhibits are included in the Evidence Appendix (ix) as Exhibits 1-5. The exhibits show that from a date prior to the present priority date to as late as 2003, glucocorticosteroid-containing therapeutics were routinely prescribed for fixed-dosage use twice per day as maintenance therapy, with the patient forbidden to vary daily dosage outside that regimen for any reason, even if experiencing an acute attack. Once one understands how inhaled glucocorticosteroids such as budesonide were typically prescribed for asthma patients prior to Appellant's invention, it is apparent that Appellant's (and not the Examiner's) interpretation of Carling *et al.* is the one that a person of ordinary skill would have taken from this reference.

Certain sections of Exhibits 1-3 have been circled and labeled in the margin with a capital letter for ready reference.

The glucocorticosteroid budesonide is the sole active ingredient in an inhaler sold under the trademark Pulmicort® Turbuhaler® for maintenance treatment of asthma. A copy of a 1997 product insert packaged with the Pulmicort® Turbuhaler® product is submitted as Exhibit 1. Recommended starting doses and highest recommended doses for various categories of patients are set out in a table in this document (Exhibit 1, page 4, section marked "A"); each and every one of these doses is to be administered "twice daily." There is no provision for additional doses to be taken "as needed," or upon acute attacks, or when encountering asthma-inducing conditions, or for any other reason. Indeed, the section titled "Patient's Instructions for Use" on page 2 of the document (see entire bottom half of page 2) repeatedly and emphatically instructs

the patient not to take more or less than the exact dose prescribed by the physician, regardless of whether the patient is feeling better or worse on a given day.

The patient's instructions concerning dosage (labeled as section "B" on page 2 of Exhibit 1) are quoted in their entirety below:

DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your Pulmicort Turbuhaler
- **DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises.
- It may take 1 to 2 weeks or longer before you feel maximum improvement so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER**, unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose.

(Emphasis in original). These instructions provide objective evidence that the paradigm for treatment of asthma with budesonide in 1997 was for a physician to prescribe a particular number of doses (generally two) per day for a patient and instruct the patient to take exactly that number of doses, no more or less. The third and last bullet points of the above-quoted instructions are particularly telling. Under no circumstances was the patient to take more doses than the specific number prescribed by the physician. Even if the patient missed a dose, the patient was not to take even a single extra dose. This is directly contrary to the Final Office Action's above-quoted assertions that

> The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is for reasonable expectation of successfully achieving maximum benefit in the treatment of any level of the asthma condition, including an increase in asthma symptoms, acute asthmatic condition, maintenance treatment, and common asthma triggers. Additionally, due to the urgency of therapy during an asthma attack, a patient would obviously seek relief with the medication without consulting with the physician, in knowing the safe daily dosage range of each medication.

Exhibit 1 also says:

> **Patients should take the medication as directed and use PULMICORT TURBUHALER at regular intervals twice daily since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician....If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician.** (Exhibit 1, page 3, section C.)

This further illustrates that the physician, and not the patient, determines when the dosage of budesonide can be altered for a given patient. If the patient suffers an exacerbation of symptoms, he must turn to a different type of medication (a short-acting bronchodilator) for immediate relief: **"PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma."** Exhibit 1, page 2, section "D".

"PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required." Exhibit 1, page 1, section "E".

"If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur." Exhibit 1, page 3, section "F".

"Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose." Exhibit 1, page 3, section "G". ("HPA (hypothalamic-pituitary-adrenal) dysfunction" is a serious side-effect of glucocorticosteroid overdosing.)

These warnings make it clear that budesonide was understood to be useful for long-term prevention of asthma symptoms when used regularly in a fixed dose that is set (and carefully monitored) by the physician according to the patient's needs, but had no role in short-term relief

of acute symptoms. According to these instructions, the only medication that could be taken by the patient on an as-needed basis was a short-acting bronchodilator. The physician was explicitly directed to ensure that the patient received the lowest effective fixed dose of budesonide. Even in 1997 (four years after Carling *et al.*), instructing the asthmatic patient to take additional doses of a budesonide composition on an as-needed basis, *i.e.,* at the patient's own discretion, was strictly forbidden. There was no evidence that taking budesonide more frequently or in larger doses than prescribed would be of any benefit to the patient, and there was a significant risk of harm. Thus, Exhibit 1 is a potent teaching-away from the presently claimed invention.

Rather than acknowledge that the budesonide product insert of Exhibit 1 would have taught away from the presently claimed methods, or explain why she believes it would not have done so, the Examiner simply dismisses the Exhibit 1 evidence as "not a true comparison of the claimed invention." According to the Final Office Action at page 15,

> The Examiner maintains the previous arguments and repeats that the evidence provided in Exhibit 1 is <u>not a true comparison of the claimed invention</u> because the Exhibit 1 is administration of budesonide as the sole active ingredient, while the claimed invention is an admixture of budesonide and formoterol. Although the Applicant's argue that the evidence is a teaching away and not a showing of unexpected results, a true comparison can not be made between the sole product and a combination.... In order to truly compare the two compositions both compounds need to be present. (Emphasis and informal English in the original.)

The Final Office Action cites no authority for the position that a prior art teaching-away can be ignored solely because it pertains to only one of the two ingredients used in the claimed method, so is not a "true comparison." Appellant maintains that the standard for a teaching away as promulgated in the courts has no such rule, but rather is pragmatic. For example, the Supreme Court, in a case where nonobviousness was found based in part on a teaching away in the art, has said, "Known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39 (1966). It is certainly true in the present case that the "known disadvantages" of administering budesonide in an acute asthma attack would have discouraged the use of budesonide plus a second agent to treat acute asthma attacks. See also *Takeda Chemical*

Industries, LTD. v. Alphapharm PTY., LTD., 492 F.3d 1350, 1358-9 (Fed. Cir. 2007), which relied heavily on the teaching-away in a published article ("Sodha II") regarding the negative side effects of a prior art compound ("compound b") in finding that it would not have been obvious to select compound b and modify it to end up with the claimed compound, pioglitazone. Even though one might characterize compound b as "not a true comparison" with pioglitazone, since the two are indeed different, the Federal Circuit said that Sodha II was properly relied upon as a teaching-away because its teachings about the negative properties of prior art compound b "would have directed one of ordinary skill in the art away from that compound" as a starting compound, and thus away from making pioglitazone. *Id* at 1359.

The Federal Circuit described the standard for a teaching away as follows: "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent from the path that was taken by the applicant." *Optivus Tech., Inc. v. Ion Beam Applications S.A.,* 469 F.3d 978, 989 (Fed. Cir. 2006). Appellant submits (and the Examiner has not denied) that one of ordinary skill, upon reading the Exhibit 1 product insert for Pulmicort Turbuhaler, would be led in a direction divergent from the path that was taken by Appellant. The product insert taught those of ordinary skill that this budesonide-containing product should not be inhaled more than twice per day, never "as needed," and never altering the dose without a physician's specific instruction, as doing so was both pointless and risky. These warnings, which stem at least in part from the recognized dangers of overdosing on corticosteroids, are consistent with Carling *et al.*'s teachings that the budesonide/formoterol combination should be inhaled just twice per day: "a twice daily dosing regime as a basic treatment of asthma" (Carling *et al.* at page 4, lines 20-21); "the intended dose regimen is a twice daily administration" (Carling *et al.* at page 6, lines 22-23). Since the prior art of record consistently led one of ordinary skill "in a direction divergent from the path that was taken by the applicant," it meets the Federal Circuit's standard for a *teaching away*, as set out in *Optivus Tech. v. Ion Beam Applications*. Given this *teaching away*, one of ordinary skill in the art would have had neither a motivation to carry out the presently claimed methods nor a reasonable expectation of success upon doing so.

That 1997 product insert pertains to budesonide alone, rather than a combination product. There are now at least two combination glucocorticosteroid/bronchodilator inhalation products (comparable to the combination product disclosed by Carling *et al.*) on the market for treatment of asthma. Product inserts for the two marketed products are presented as Exhibits 2 and 3. Although neither of these product inserts is prior art to the present application, they nevertheless illustrate how those of skill in the art used glucocorticosteroid/bronchodilator combination products even years after the present application's priority date: i.e., the physician instructs the patient to inhale a set dose, twice per day--consistent with Appellant's (and not the Examiner's) interpretation of Carling *et al.*

The first combination product is the most relevant, as it is for Symbicort® Turbuhaler®, a budesonide/formoterol inhalation product similar to that disclosed by Carling *et al.* Exhibit 2 is a product insert circa 2001 for that product. It says that the "**recommended dosage**" is 1-2 inhalations twice daily (Exhibit 2, page 1, section "A"); when control of symptoms is achieved with the twice daily regimen, the physician can choose to reduce the number of inhalations to one daily (Exhibit 2, page 1, section "B").

The insert instructs the physician to adjust the dosage to reflect the severity of the particular patient's disease: "**The dosage of the components of Symbicort Turbuhaler is individual and should be adjusted to the severity of the disease. This should be considered when treatment with combination products is initiated.**" Exhibit 2, page 1, section "C".

There is no suggestion anywhere in the document that the patient can be instructed to take it "as needed," e.g., when experiencing an acute asthma attack. To the contrary, use outside of the fixed dose is dangerous and forbidden: "**If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought.**" Exhibit 2, page 2, section "D".

Moreover, "**increasing use of rescue bronchodilators** [i.e., a short-term bronchodilator, not the Symbicort® Turbuhaler® budesonide/formoterol combination] **indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy**"; "**patients should be regularly reassessed by a doctor, so that the dosage of Symbicort Turbuhaler remains optimal. The dose should be titrated to the lowest dose at which effective control**

of symptoms is maintained." Exhibit 2, page 2, section "E"; and page 1, section "F", respectively (emphasis added).

These instructions clearly indicate that if the patient experiences an increase or decrease in symptoms, the patient is to notify the physician so that the maintenance treatment protocol with Symbicort Turbuhaler can be reassessed (and if necessary, adjusted up or down) by the physician. Adjusting the dosage from day to day at the patient's discretion is nowhere contemplated.

Rather than acknowledge that Exhibit 2 provides evidence that one of ordinary skill in the art in 2001 (and presumably also prior to that, at the 1998 priority date) would not have prescribed the budesonide/formoterol combination for use in accordance with the present invention, the Final Office Action at pages 15-16 asserts that Exhibit 2 shows "it is not impossible to take an additional administration,"[1] and says that Exhibit 2 "verifies the Examiner's statement that patients will take more than the current dose if needed":

> In regards to Exhibit 2, the statements D and E verifies the Examiner's statement that patients will take more than the current dose if needed. Although the additional doses are not recommended, it is not impossible to not take an additional administration if the patient *feels the need* for treatment. In an asthma attack, if a patient is faced with not breathing and taking an additional administration within the safe inhalation amounts, one would find that the patient would take an as-needed administration. To clarify further, the insert obviously address the patients that use the medication "as needed", thus proving that patients will use the medication "as needed" even though it is not recommended. In other words, the statements in D and E show evidence that patients will take additional medication when needed without the doctor's advice. (Emphasis in the original)

First, Appellant points out that U.S. law does not require Appellant to show that something is "impossible" in order to prove that it is not obvious. Nor is the proper question whether some patient somewhere might ignore instructions regarding proper use of the Symbicort product for maintenance treatment in accordance with the Exhibit 2 product insert, and accidently or intentionally take a larger dose than his/her physician prescribed. The hypothetical possibility of additional doses that might be inhaled despite the instructions in

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[1] The Final Office Action actually says "not impossible to not take an additional administration," but given the context, Appellant presumes the Examiner meant "not impossible to take an additional administration."

Exhibit 2 is simply irrelevant to an obviousness analysis. Instead, the focus should be on whether those of ordinary skill in the art would have believed it obvious to administer the budesonide/formoterol product in the manner claimed, given what was known in the art at the priority date. Exhibit 2 is provided as evidence that a physician or other person of skill in the art in 2001 (and presumably at the 1998 priority date as well) would have known not to administer, or to allow the patient to administer, doses of the budesonide/formoterol combination other than the recommended two maintenance doses per day.

Second, it is unclear why the Examiner believes that the statements in sections D and E of Exhibit 2 "verifies the Examiner's statement that patients will take more than the current dose if needed" and "obviously address the patients that use the medication 'as needed', thus proving that patients will use the medication 'as needed' even though it is not recommended." Appellant does not see support for these assertions in either section D or section E. By saying that if a patient exceeds the current dose of Symbicort, "medical attention must be sought," section D quite clearly communicates that exceeding the current dose is potentially dangerous and is not to be done under any circumstances. It cannot be interpreted as "proving that patients will use the medication 'as needed'." Section E mentions "increasing use of rescue bronchodilators," but that refers not to the Symbicort budesonide/formoterol combination, but rather an entirely separate category of inhaled bronchodilator drugs, the short-acting β2 agonists. Inhalers containing such short-acting β2 agonists are typically prescribed in addition to, and separate from, whatever maintenance treatment is prescribed. The patient is told to use the short-acting β2 agonist inhaler as needed, whenever he feels an attack is imminent, or if he is about to encounter symptom-inducing conditions (such as exercise or allergens). Section E is saying that increasing use of these short-acting β2 agonists (i.e., not Symbicort) indicates that the patient's overall asthma symptoms are worsening. Worsening symptoms in turn suggest that the patient's ongoing twice-daily maintenance treatment with Symbicort is not working as well as it should, so should be reassessed by the physician and perhaps adjusted by increasing the maintenance dosage or changing to a different maintenance medication. Thus, the statements in sections D and E do not even imply that the patient should use Symbicort (as opposed to a short-acting β2 agonist) on an as-needed basis. In fact, by saying that "medical attention must be sought" if the

patient exceeds the prescribed dose of Symbicort, the quoted statements plainly imply the opposite.

Consistent with the teachings about budesonide in Exhibit 1 discussed above, Exhibit 2 makes it clear that the combination product in Symbicort Turbuhaler was to be administered as a regular maintenance treatment just twice per day, and if the patient suffered any acute asthma attacks despite this maintenance treatment, she was to use a different drug, a short-acting β2 agonist (not the Symbicort combination), as needed to relieve her symptoms. Thus, nothing in Exhibit 2 "verifies" the Examiner's unwarranted assumption that patients would take additional doses of the Symbicort product "if needed."

The second combination product is the Advair Diskus® fluticasone propionate/salmeterol xinafoate inhaler. Like the Symbicort Turbuhaler combination product, the Advair Diskus combination product is prescribed for use twice per day, at a dose set by the physician. (Like budesonide, fluticasone propionate is a glucocorticosteroid, and like formoterol, salmeterol xinafoate is a beta-2 agonist.) The Patient's Instructions for Use (March 2003) for this product, attached as Exhibit 3, emphasizes repeatedly that the product must be used neither more nor less often than instructed by the physician. The pertinent portion of these instructions, found on page 2 of the insert, is reproduced below:

2. It is important that you inhale each dose as your doctor has advised. The label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. **Do not use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time.**

3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder **that most, but not all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of medicine, you should not exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. If you are not sure you are receiving your dose of ADVAIR DISKUS, contact your doctor or pharmacist.

4. You may feel better after the first dose of ADVAIR DISKUS; however, it may take 1 week or longer to achieve maximum benefit. It is **IMPORTANT THAT YOU USE ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.

5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.

6. **DO NOT USE ADVAIR DISKUS TO *RELIEVE* SUDDEN ASTHMA SYMPTOMS** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma). **An inhaled, short-acting bronchodilator such as albuterol should be used to *relieve* sudden asthma symptoms.** If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should continue to take ADVAIR DISKUS as instructed by your doctor.**

The patient is adamantly instructed not to use the combination therapy more frequently than 2 times daily, spaced approximately 12 hours apart, and is told to inhale only the recommended dose of 1 inhalation each time. The patient is further instructed not to use the product to relieve sudden asthma symptoms.

Like the Exhibit 2 evidence discussed above, this evidence (from 2003) is directly contrary to the Examiner's assertions regarding what would have been "obvious" to one of ordinary skill in the art ten years earlier, in view of Carling *et al.* Although Exhibit 3 is not prior art, it is submitted as evidence that those of ordinary skill in the art still understood, even years after the present priority date, that glucocorticosteroid/ bronchodilator combinations were used as maintenance treatment only, and were never used to relieve asthma attacks.

Rather than address Appellant's position on the merits, however, the Examiner has consistently dismissed the evidence in Exhibit 3 because it concerns compounds other than budesonide and formoterol. See the Final Office Action at page 16: "In order to truly compare the two compositions both compounds need to be present. It is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention." Appellant has pointed out repeatedly during prosecution that Exhibit 3 is not being cited as "unexpected results" (so the "commensurate in scope" issue is irrelevant) and that one need not "truly compare" the Exhibit 3 composition with the composition utilized in the present claims in order to understand the point being made by Appellant in providing Exhibit 3, **i.e., that those of ordinary skill in the art, even years after the present application's 1998 priority date, understood that glucocorticosteroid-containing compositions in general should not be administered "as needed" or to relieve an acute asthma attack**. Exhibit 3 helps show that what is "obvious" to the Examiner in view of Carling *et al.* certainly would not have been obvious to one of ordinary skill in the art who does not have the benefit of the information in Appellant's disclosure. Unfortunately, rather than addressing that point on the merits, the Examiner persists in simply dismissing the Exhibit 3 evidence for what Appellant submits are inappropriate reasons.

Further evidence concerning the proper interpretation of Carling *et al.* is provided by the publication submitted herewith as Exhibit 5 (Barnes, "A Single Inhaler for Asthma?" *Am J Respir Crit Care Med* 171:95-96, 2005), originally made of record as an Exhibit submitted with

the Amendment filed July 27, 2007. Exhibit 5 is an editorial commenting on an article (O'Byrne *et al.*, "Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma," *Am J Respir Crit Care Med* 171:129-136, 2005) that appeared in the same journal. (The O'Byrne et al. article itself, which reports a successful clinical study comparing Appellant's presently claimed method to the prior art method disclosed in Carling *et al.*, is submitted herewith as Exhibit 4 and is discussed in detail below, in the context of objective evidence of nonobviousness.)

In the Exhibit 5 editorial, Barnes states his opinion that **"the study by O'Byrne and his colleagues may lead to changes in the paradigm of asthma management...."** (Exhibit 5, page 95, last paragraph, emphasis added.) This suggests that Barnes (a physician with particular expertise in the treatment of asthma) did not regard the presently claimed method to have been a mere obvious variation on the standard Carling *et al.* method (in which the budesonide/formoterol combination was used solely for twice-daily maintenance treatment). Barnes explains in the carryover sentence of col.1-2 one reason why the new approach (i.e., Appellant's method) was not previously contemplated: **"A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid."** (This explanation is significant in that it shows the correctness of Appellant's position regarding why one of ordinary skill would not have used Carling *et al.*'s combination inhaler on an as-needed basis.) Barnes then notes that, based on O'Byrne *et al.*'s results, this concern turned out not to be a problem in practice: in fact, the O'Byrne *et al.* patients instructed to take the budesonide/formoterol combination on an as-needed basis inhaled on average only one additional dose per day. Even though there was only one additional dose inhaled per day on average, this approach was found to be significantly more effective in preventing exacerbations than a fourfold higher fixed daily maintenance dose of budesonide. Barnes opines that these are "surprisingly good results" (page 95, col.2, first full paragraph).

And Barnes is not the only expert to recognize the paradigm-changing nature of the presently claimed methods. According to D'Urzo, "Inhaled Glucocorticosteroid and Long-Acting β2-Adrenoceptor Agonist Single-Inhaler Combination for Both Maintenance and Rescue Therapy: A Paradigm Shift in Asthma Management," Treat Respir Med 5:385-391 (2006), a

publication originally made of record in the Amendment filed June 3, 2010, and presently included in the Evidence Appendix as Exhibit 6,

> **The use of a single inhaler (budesonide/formoterol) for both maintenance and reliever therapy represents a significant paradigm shift in asthma management that is simple and effective.** (page 389, last paragraph)

D'Urzo refers to this as "**a novel strategy**" (page 390, first full paragraph), and opines:

> **The concept of single-inhaler maintenance and reliever therapy represents one of the most important advances in asthma management in many years, and one that appears particularly well suited for utilization in the primary care setting.** (page 390, last paragraph)

Plainly neither D'Urzo nor Barnes (both experts in the field) viewed use of a budesonide/formoterol combination in accordance with the present claims to have been "obvious" in view of standard asthma therapy, i.e., therapy in which a glucocorticosteroid (whether alone or in combination with a second agent) is used solely for maintenance treatment, never as-needed as a reliever. It is to be kept in mind that these statements by D'Urzo and Barnes, including their characterizations of the claimed method as "changes in the paradigm of asthma management," "a significant paradigm shift" and "one of the most important advances in asthma management in many years," were made over a decade after the Carling *et al.* reference was published. In the heavily researched field of asthma treatment, if Appellant's invention had indeed been "obvious" from Carling *et al.*'s teachings, it would not, over a decade later, have been regarded as the radical departure from the norm implied by the Barnes and D'Urzo articles. Thus, the Barnes and D'Urzo articles provide further evidence supporting Appellant's position that those of skill in the art understood at the 1998 priority date that a budesonide/formoterol combination should not be administered "as needed," but rather only in the regular, twice-daily maintenance protocol described in Carling *et al*.

The Final Office Action at page 17 purports to have considered the comments made by Barnes, "but does not find that the evidence overcomes the prior art for the reasons stated above and below." Appellant can find no reasons specifically addressing Barnes either "above" or "below" in the Final Office Action, so do not have the Examiner's views on why this evidence is not believable or does not overcome the rejection. With respect to D'Urzo, all that the Final Office Action says is

> The Examiner does not find Appendix E [D'Urzo] persuasive to overcome the art because given above.[2] First, the Carling et al. method is effective in treating asthma. Although the additional doses are not recommended, it is not impossible to not take an additional administration if the patient *feels the need* for treatment. In an asthma attack, if a patient is faced with not breathing and taking an additional administration within the safe inhalation amounts, one would find that the patient would take an as-needed administration. (Page 19, emphasis in the original.)

The Final Office Action then goes on to repeat the Examiner's characterization of another reference, the Symbicort Turbuhaler product insert (Exhibit 2), but says nothing more about the D'Urzo article. Thus, the Examiner provides no clue as to why she believes D'Urzo's objective assessments that the claimed method provides "a significant paradigm shift" and is "one of the most important advances in asthma management in many years" are not dispositive of nonobviousness. The Final Office Action's offhanded observation that "the Carling et al. method is effective in treating asthma" is not on point, where the question is the remarkable and unexpected improvement over the Carling *et al.* method that is provided by the presently claimed method and that is now recognized with praise by experts in the field.

The Supreme Court in *Graham* explained that, to reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the Appellant's invention was unknown and just before it was made. "The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991). In view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person of ordinary skill at the time of the invention. MPEP 2141.03.

The evidence discussed above (particularly the prior art teaching away in Exhibit 1 and the comments of experts in Exhibits 5 and 6) help to establish what was known by those of ordinary skill in the art at the time of Carling *et al.* and at the filing date of Appellant's application. With this level of ordinary skill in the art in mind, Appellant turns to the question of whether the Examiner has met her burden of establishing (1) that there would have been a reason

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[2] It is not clear to what this "because given above" is meant to refer. None of the arguments in the Final Office Action preceding this quoted passage refer even generally to D'Urzo or to the above-quoted language from D'Urzo.

to alter the teachings of Carling *et al.* in order to arrive at the presently claimed methods (*KSR International Co. v. Teleflex Inc. et al.,* 127 S.Ct 1727, 1741 (2007); and (2) that one of ordinary skill in the art would have reasonably expected the claimed invention to work *(Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.,* 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)), both being essential elements of any *prima facie* case of obviousness. These elements are addressed in turn.

Reason to alter the teachings: The Examiner's position regarding a reason (i.e., motivation) to alter the teachings is set forth at pages 8-9, 13-14, and 17 of the final Office Action. Appellant understands the Examiner's position to stem in part from a combination of certain interpretations of Carling *et al.*, which Appellant restates as follows:

(a) the Examiner's deduction that the maximum dosage recommended by Carling *et al.* at page 6, lines 24-27, can be divided into eight separate inhalations;

(b) the Examiner's conclusion that, because her hypothetical eight inhalations add up to no more than Carling *et al.*'s maximum suggested daily dose of formoterol and budesonide, all eight could be "safely inhaled" by any patient on any given day, at the patient's discretion;

(c) the Examiner's interpretation of Carling *et al.*'s statement on page 6, lines 27-29, that "[the] particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)" to mean that the <u>patient</u> can make the determination of his/her dosage on any given day, varying the dosage from one to a total of eight inhalations each day; and

(d) the Examiner's view that Carling *et al.*'s repeated statements that the composition should be administered <u>twice per day</u> would be ignored by one of ordinary skill because, in the Examiner's opinion, the reference does not "completely eliminate" administration of additional doses.

Appellant believes these interpretations of Carling *et al.*'s teachings are not accurate representations of how one of ordinary skill in the art of asthma treatment would have read this reference. For example, the Examiner has made the unwarranted assumption (paraphrased in part (b) above) that every asthma patient will be able to "safely inhale" even the high end of the ranges of "suitable daily doses" set forth at page 6, lines 24-27, of Carling *et al.* (the ranges

being 6-100 μg of formoterol and 50-4800 μg of budesonide). Even if Carling *et al.* hadn't gone on to explain that the "particular dose" depends "strongly" on patient-specific factors ("the particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)," one of ordinary skill in the art of asthma treatment would clearly not have read Carling *et al.*'s teachings about dosage ranges as meaning all patients can safely inhale all doses up to and including the maximum. That simply is not reasonable. Young children, for example, would not be able to safely inhale the same daily dosage that a 200 lb. adult could handle. Further, the Examiner's assumption is inconsistent with the knowledge in the art that steroids in general were potent drugs with potentially dangerous side effects, whose use was necessarily carefully monitored in every patient to avoid overdosing (see evidence to that effect in Exhibits 1-5, as discussed above).

Appellant has previously explained why the Examiner's interpretation of Carling *et al.*'s statement quoted in part (c) above is far off-base. Carling *et al.*'s reference to "severity of the disease" as being one of the bases for setting the amount of the twice-daily dose of the composition does not mean that the patient should choose to take more doses if his/her symptoms are particularly severe on a given day. It simply means that the overall level of the patient's chronic disease is one of the factors (along with the patient's age, weight, etc.) the prescribing physician should take into account in setting the twice-daily maintenance dose. (It stands to reason that a patient who has debilitating chronic asthma will be prescribed a higher maintenance dose than a patient who suffers only mild discomfort readily controlled by a low maintenance dose.) Thus, this statement in Carling *et al.* about severity of the disease cannot be read as providing any motivation to discard what was widely known about glucocorticosteroid treatment and instead give the patient free rein to inhale additional doses of the composition as needed, as determined by the patient; or when the patient expects to encounter an asthma inducing condition; or when the patient experiences an acute asthma attack, as required by the present claims.

Appellant's understanding of the Examiner's assumption paraphrased in part (d) above is derived from the Final Office Action at page 17. It appears that the Examiner is relying at least in part on this interpretation of Carling *et al.* as a justification for brushing aside Carling *et al.*'s explicit recommendations regarding use of the composition just twice per day, i.e., as a regular

maintenance treatment. Under the Examiner's theory as stated on page 17 of the Final Office Action, the reference would have to "completely eliminate a patient taking more than two administrations a day" in order to be interpreted as truly teaching administration just twice per day. The fact that Carling *et al.* explicitly says to administer twice per day seems largely irrelevant to the Examiner, since the Examiner would apparently require that the reference also specify not to administer more than twice per day. The Examiner's view is despite the evidence of record, discussed above, revealing that it was widely known at the priority date that budesonide and other glucocorticosteroids are not bronchodilators; are useful only for regular maintenance therapy, not as-needed use; and are potentially dangerous if the dosage is not tightly controlled by the physician. Appellants have provided multiple lines of evidence to prove these points, including the *teaching-away* prior art of Exhibit 1 and the post-filing date publications of Exhibits 2-6; the Examiner has dismissed each as either "not a true comparison" or "not commensurate in scope with the claimed invention," or for failing to show that it is "impossible" to take the additional administrations--or for reasons that unfortunately have not been placed in the record, so remain a mystery. Appellant submits that none of these bases for dismissing Appellant's evidence comports with the law.

The final Office Action's discussion of motivation at page 9 concludes with a statement that apparently springs from the Examiner's own beliefs regarding asthma therapy in general, as it is not found in the cited art: "due to the urgency of therapy during an asthma attack, a patient would obviously seek relief with the medication without consulting with the physician, in knowing the safe daily dosage range of each medication." This reflects a misunderstanding of the nature of the "medication" disclosed in Carling *et al.* and required by the present claims. While it is certainly true that asthma patients were commonly given inhalers for emergency use during asthma attacks, and were told they can seek relief using those inhalers without consulting with the physician each time, the medication in those emergency inhalers was a short-acting bronchodilator, never a steroid or a combination containing a steroid. Steroids were considered to be useless for emergency use against an asthma attack, as they are not bronchodilators. The role that steroids played in asthma therapy at the time of the invention is as slow-acting anti-inflammatory agents that are useful in controlling bronchial inflammation over the long term, if taken regularly (not just sporadically) as long-term maintenance therapy. So, even if a steroid

such as budesonide were regarded as perfectly safe, there would have been no point (prior to the present invention) in telling a patient to take a budesonide-containing medication to alleviate his/her asthma attack. The sensible medication to take for that purpose would contain only a fast-acting bronchodilator, and not a useless second agent. Since steroids in general were considered potentially risky and were typically administered under strict controls to prevent overdosing (see the evidence in that regard discussed above), it would have been not only pointless but also unthinkable to include a steroid in an inhaler given to a patient for emergency use whenever the patient felt the need. Thus, though the Examiner may believe it obvious to use Carling *et al.*'s budesonide-containing medication to alleviate asthma attacks, this is not a belief that would have been shared by one of ordinary skill in the art at the time of the invention.

Carling *et al.* teaches twice-daily maintenance therapy with the formoterol/budesonide combination. Those of ordinary skill in the art would have recognized that Carling *et al.* taught use of that combination only for maintenance therapy. Without a motivation to alter Carling *et al.*'s teachings to arrive at the presently claimed methods, the obviousness rejection fails.

Expectation of Success: A passage in the Final Office Action that seems to communicate the Examiner's view regarding "expectation of success" is on page 14:

> It is noted by Carling et al. that the combination of formoterol with budesonide is well known to be beneficial for the treatment of asthma (see page 4, lines 4-21). Moreover, if the patient is experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, the patient can still safely inhale an additional 6 inhalations without going over the maximum suitable daily dosage. In general, Carling et al., teaches therapeutic relief from asthmatic attack. The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is for reasonable expectation of successfully achieving maximum benefit in the treatment of any level of the asthma condition, including an increase in asthma symptoms, acute asthmatic condition, maintenance treatment, and common asthma triggers. (Non-standard English in original)

As Appellant understands it, the Examiner is saying that one of ordinary skill would have a reasonable expectation of successfully treating any and all asthma patients by simply handing them an inhaler containing Carling *et al.*'s formoterol /budesonide composition and telling them to inhale any amount per day that they wish, up to and including the maximum daily dose of

100 μg formoterol and 4800 μg budesonide, because that will give them "maximum benefit." Appellant points out that Carling *et al.* warns the reader that the proper fixed daily dose of the combination "will strongly depend" on patient-specific factors, factors that are not normally left to the judgment of the patient. Further, at least with respect to the budesonide part of this composition, Appellant has provided ample additional evidence that one of ordinary skill in 1998 would NOT have had a reasonable expectation of success under the scenario the Examiner believes is "obvious." In fact, the very idea would have shocked the medical establishment. (See above discussion of Exhibit 1.) This view apparently had not changed by 2001, according to the 2001 product insert (Exhibit 2) packaged with the formoterol/budesonide combination product Symbicort Pulmuhaler. This product insert warned the user not to exceed the fixed, twice-daily dosage prescribed by the physician. (See above discussion of Exhibit 2.) Even in 2003, a product insert for another glucocorticoid/ bronchodilator combination product gave similar warnings. (See above discussion of Exhibit 3.) In 2005, an expert in the field of asthma (Barnes) offered an explanation of why the Appellant's paradigm-changing method had not been previously employed: **"A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid."** (See above discussion of Exhibit 5.) The Examiner has offered not a single shred of objective evidence to support her views, to counter the multiple lines of evidence supplied by Appellant proving that one of ordinary skill at the 1998 priority date would not have had a reasonable expectation that the claimed methods would succeed. Rather, the Examiner simply offers her own unsupported opinion in this regard. Thus, the *prima facie* case of obviousness must fail.

The above evidence and arguments demonstrate that the Examiner has not met her burden in making out a *prima facie* case of obviousness. Accordingly, it is unnecessary for Appellant to come forward with further objective evidence to rebut the Examiner's case. However, such evidence is already of record, so Appellant will bring it to the Board's attention as a further (and powerful) indication of the non-obviousness of the presently claimed methods. Such objective evidence must be taken into account by the U.S. Patent and Trademark Office. *In re Soni*.

Surprising Results

Several publications of record report significant and unexpected clinical benefits with the methods of the invention, compared to Carling *et al.*'s method as well as other methods of treating asthma.

First, Appellant points to the objective evidence of surprising results embodied in Exhibit 4, the O'Byrne *et al.* journal article briefly mentioned above. The authors of that study conducted clinical trials to compare three different treatment regimens for asthma. The relevant features of the Study Design (page 130, first column) are summarized here:

In the first treatment arm (nicknamed "**bud/form maintenance + relief**") of the O'Byrne *et al.* study, the patients were instructed to use a budesonide/formoterol combination inhaler twice per day, every day, for maintenance, plus the same inhaler for relief of symptoms on an as-needed basis, as determined by the patient. This first treatment arm was thus instructed to administer the combination in accordance with the present claims.

Patients in the second treatment arm ("**bud/form + SABA**") were instructed to use a budesonide/formoterol combination inhaler just twice per day, and no more: *i.e.*, for maintenance therapy only. A second inhaler containing a different drug, the short-acting bronchodilator terbutaline, was provided to the patients of this second treatment arm for use as needed for immediate relief of acute asthma symptoms. Since this second treatment arm received the budesonide/formoterol combination just twice per day, as explicitly taught by Carling *et al.*, it is representative of the closest prior art identified by the Examiner.

Patients in the third treatment arm ("**bud + SABA**") were instructed to use a high dose of budesonide from a budesonide-only inhaler just twice per day (a fourfold higher budesonide dose than the dose used in the second treatment arm). For relief of acute symptoms, these patients used a second inhaler containing terbutaline as needed. This third treatment arm thus represents the prior art such as in the Pulmicort Turbuhaler® 1997 product insert of Exhibit 1, in which a budesonide-only inhaler was used for maintenance therapy twice per day, and the patient was instructed to use a separate bronchodilator product as needed for relief of acute symptoms (see the section labeled "I" on page 2 of Exhibit 1).

As shown in the first bar graph of Figure 1B of O'Byrne *et al.*, patients who used the combination inhaler in accordance with the present claims dramatically decreased the total

number of severe exacerbations (acute asthma attacks) experienced by those patients, compared to the total number experienced by patients who were in either the second or third treatment arm. Table 2 analyzes the data in another way: only 16% of the patients instructed in accordance with the present claims experienced severe exacerbations, compared to 27% or 28% of the patients in the second and third treatment arms, respectively. Similarly striking differences were seen in many other measures described in detail in the Results section on page 130, in Figures 1 and 2, and in Table 2. It is telling that an expert physician not involved in the O'Byrne clinical trial (Barnes, discussed above) characterized the 2005 O'Byrne *et al.* study as showing "**surprisingly good results**" for the presently claimed methods compared to the prior art methods (Barnes (Exhibit 5) at page 95, col.2, first full paragraph). If the results were surprising in 2005, they certainly would have been considered surprising at the present application's 1998 priority date. It is therefore irrefutable that the presently claimed method produces results that are unexpectedly better than what the Carling *et al.* prior art method produces.

Despite this evidence, the Examiner maintains her view that the O'Byrne *et al.* results are not surprising:

> In regards to Exhibits 4 and 5, the Examiner has considered the comments made by O'Byrne et al. and Barnes, but does not find that the evidence overcomes the prior art for the reasons stated above and below. Carling et al., teaches that the combination of budesonide and formoterol have greater efficiency and duration of bronchodilator action, and rapid onset action, which provides rescue medicine, adequate dosing for treating asthma (see page 4, lines 4-21), thus the Applicant's results are not viewed as surprising. Final Office Action at page 17.

Appellant points out that any teachings of Carling *et al.* regarding advantages of the budesonide/formoterol combination are advantages resulting from use of the combination in the treatment method explicitly taught by Carling *et al.* (*i.e., just twice daily*), in comparison with other asthma treatments that were then known in the art. Carling *et al.* did not contemplate supplementing the described twice-daily treatment with additional "as needed" use of the budesonide/formoterol combination, and certainly did not provide any reason to believe there might be <u>further</u> advantages, in addition to those disclosed for use of the combination twice daily, if one were to use the combination not only twice daily but also take additional inhalations as needed. Appellant has provided several lines of evidence proving that use of the budesonide/

formoterol combination as both a maintenance treatment and a reliever medication inhaled as needed, as determined by the patient, provides dramatically and surprisingly better results when directly compared to use of the same combination in accordance with Carling *et al.*'s teachings, i.e., for twice-daily maintenance treatment alone (with a separate, short-acting β2 agonist bronchodilator inhaler employed as-needed for emergencies). Thus, the surprising results reported by O'Byrne *et al.* are in addition to any advantages taught by Carling *et al.* for twice-per-day maintenance treatment alone. The significance and surprising nature of these results cannot be dismissed, as the Examiner has done, merely because Carling *et al.* said that twice-per-day maintenance treatment with the combination had advantages compared to other treatments then known in the art. Nothing that Carling *et al.* said about advantages with twice-per-day dosing with the budesonide/formoterol combination could have led one to expect the further, and quite striking, improvements seen in several measures of efficacy (such as the rate of exacerbations) in the second group of patients. The Examiner has not explained what in Carling *et al.* would have led one of ordinary skill in the art to expect these further improvements when the Carling *et al.* combination is utilized in a way that was not contemplated by Carling *et al.*, particularly in view of the understanding in the prior art that budesonide and other glucocorticosteroids were not useful for immediate relief of symptoms and should not be administered on an as-needed basis.

Three other published clinical studies, all previously submitted in this application with the Amendment filed June 3, 2010, provide yet more evidence of surprising results. Of particular note is Kuna *et al.*, "Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations," Int J Clin Pract 61:725-736 (2007), enclosed as Exhibit 7 in the Evidence Appendix. As in O'Byrne *et al.*, the Kuna *et al.* study showed a remarkable reduction in asthma exacerbations achieved with treatment in accordance with the claimed methods, compared to treatment in accordance with Carling *et al.*'s twice-per-day maintenance regimen. The new study investigated whether this reduction in exacerbations might be attributable to the fact that patients treated in accordance with the claimed methods ultimately received a higher total daily dose of budesonide/formoterol than those on a twice-daily maintenance-only regimen. In the Kuna *et al.* study, one group of patients inhaled a maintenance dose of 160 μg budesonide and 4.5 μg formoterol fumarate dihydrate from an inhaler twice per day, every day, plus

additional inhalations of the same combination as needed for relief of asthma attacks, as determined by the patient. That treatment was referred to as "SMART" (short for "Symbicort® Maintenance And Reliever Therapy"). It is in accordance with the claimed methods. A second group of patients inhaled a maintenance dose of 320 μg budesonide and 9 μg formoterol fumarate dihydrate twice per day (i.e., double the maintenance dose given to the "SMART" group) and used terbutaline (not budesonide/formoterol) as an as-needed reliever medication. This treatment is in accordance with the method taught by Carling *et al.*; though Carling et al. did not specify use of terbutaline for reliever use, that was a standard supplement to maintenance treatment in the art. The patients in that second group, referred to by Kuna *et al.* as the "budesonide/formoterol" group, received a total of **640 μg** budesonide and **18 μg** formoterol fumarate dihydrate per day over the course of the study, compared to the average total of only **483 μg** budesonide and **13.6 μg** formoterol fumarate dihydrate per day administered to the patients of the "SMART" group. See Figure 5 on page 733.

Despite receiving an overall lower total daily dose of budesonide/formoterol (and no terbutaline at all) compared to the second group, the "SMART" group suffered far fewer severe exacerbations than did the second group. See Table 2 on page 730, which reports that the SMART group had a total of **125** severe exacerbations (adding up to a total of **692 days** of exacerbations) during the study, while the "budesonide/formoterol" group had **173** severe exacerbations, adding up to a total of **1143 days** of exacerbations. Thus, even though Kuna *et al.*'s "SMART" group received on average only 75% of the total daily dose of budesonide/formoterol received by the second group, and were given no terbutaline at all, the rate of severe exacerbations in the "SMART" group was 28% lower than the rate in the second group. ***Nothing in Carling et al., nor in any other prior art, could have predicted such a counterintuitive result.***

The Examiner does not dispute (actually, does not even address) the fact that the "SMART" group treated in accordance with the present claims achieved surprisingly better results with respect to severe exacerbations than did the control group in Kuna *et al.* Rather, the Examiner focuses on a sentence in the abstract reporting that, for certain measures other than number of severe exacerbations, all treatments were equivalent. According to the Final Office Action at pages 17-18,

> The Examiner does not find [Kuna *et al.*] persuasive to overcome the art because Kuna et al. also teaches that all treatments provided similar marked improvements in lung function, asthma control days and asthma-related quality of life (see abstract). Thus, Carling et al. still obvious reads on the claimed invention (i.e. a method of treating asthma . . . .) as discussed above. (Informal English in the original.)

It is not clear what point the Examiner is making here. Kuna *et al.* reports that the claimed method ("SMART") provides surprisingly good results compared to the Carling *et al.* method with respect to the number of severe exacerbations suffered by the various treated groups, even though the maintenance dose given to the SMART group was only 50% of the maintenance dose given to the group treated in accordance with the Carling *et al.* method, and the SMART group ended up receiving only 75% of the total amount of budesonide and formoterol received by the Carling *et al.* group. Kuna *et al.* concludes that "SMART" therapy "**reduces the incidence of severe asthma exacerbations and maintains similar daily asthma control at a lower overall drug load**." (page 735, left column). Perhaps the Examiner is assuming that the mere fact that all treatment groups maintained similar "daily asthma control" (i.e., the "lung function, asthma control days and asthma-related quality of life" factors mentioned in the abstract) allows the conclusion that Kuna *et al.*'s results overall do not qualify as "surprising." If that is the point being made in the Final Office Action, Appellant disagrees. See, e.g., *In re May*, 574 F.2d 1082 (CCPA 1978) (Evidence that the compound used in the claimed method had an unexpected property was sufficient to overcome the obviousness rejection even though the compound also had another property that was expected), and *In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective on weeds in corn and soybean crops than was the closest prior art compound was sufficient to overcome the obviousness rejection, even though the claimed compound was only an average performer on crops other than corn and soybean). Furthermore, if anything, the fact that similar "daily asthma control" was maintained despite the lower overall drug load in the SMART group simply adds to the surprising nature of the SMART results. It certainly does not negate it.

Or perhaps the above-quoted language from the Final Office Action instead was supposed to mean that, because the Carling *et al.* method "still treats asthma," the claimed method by definition cannot be patentable over the Carling *et al.* method, regardless of how

much better the claimed method might be. If that is the Examiner's position, Appellant points out that it is plainly contrary to law. Nonobviousness of an invention does not hinge on whether the prior art was nonfunctional. (See, e.g., *United States v. Adams*, 383 U.S. 39 (1966) (Battery was held nonobvious over prior art batteries that functioned but did not have the surprising advantages of the claimed battery). Appellant is not alleging that the Carling *et al.* method provides no benefit in treating asthma. Obviously it does. The presently claimed method, however, is surprisingly better than the Carling *et al.* method in a very important aspect: patients treated in accordance with the claimed treatment protocol experienced on average a much lower number of severe exacerbations (events that would typically send the patients to the hospital), even though receiving on average a significantly lower total amount of the combination drug. According to Kuna *et al.* at page 735, left column, "**the SMART approach represents a significant improvement over fixed, twice-daily combinations of higher-dose [inhaled corticosteroid/long-acting β_2-agonists], which have until now been regarded as the most effective way to manage moderate and severe persistent asthma**."

Further surprising results can be found in Rabe *et al.,* "Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study," Lancet 368:744-753 (2006) (Exhibit 8). Rabe *et al.* divided patients into three groups, all three of which received the same twice-daily maintenance treatment with a budesonide/formoterol combination inhaler, but different reliever therapies for as-needed use: one group used budesonide/formoterol not only for maintenance treatment, but also as the reliever; the second group used formoterol as the reliever; and the third used terbutaline as the reliever. Consistent with O'Byrne *et al.*'s results, Rabe *et al.* found a much lower rate of exacerbations in patients who used the budesonide/formoterol combination both for maintenance and for as-need relief (i.e., in accordance with the present claims), compared to patients in the third group who used the combination solely for maintenance (i.e., in accordance with Carling *et al.*'s teachings) and used terbutaline for as-needed relief. See Table 2 on page 748 of Rabe *et al.* The same Table 2 also shows that using the budesonide/formoterol combination as a reliever was superior to using formoterol alone as the reliever, illustrating that the benefit of using the combination as a reliever is not entirely attributable to the formoterol component of the combination. (Since formoterol is a bronchodilator and budesonide is not, it

would have been reasonable to expect the improvement seen with the combination to be entirely attributable to the formoterol part of the combination.) See also the graph in Figure 2. These results further underscore the surprising benefits obtained with the methods of the invention, compared to the Carling *et al.* method, and provide another startling observation: ***Given the teachings in the art that budesonide and other glucocorticosteroids are of no use as reliever medications because of their lack of bronchodilative effect and the long time it takes for them to exert their anti-inflammatory effects, it was particularly unexpected to find that the budesonide/formoterol combination was superior to formoterol alone as a reliever medication, when each was used in conjunction with budesonide/formoterol maintenance therapy.***

Again the Examiner is not convinced, and again for dubious reasons:

> The Examiner does not find [Rabe et al.] persuasive to overcome the art because Kuna et al. also teaches that all treatments were well tolerated (see abstract). Thus, regardless if the rate of exacerbations were lowered, the Carling et al. method still treats asthma. For reasons given above, the Examiner still reads that Carling et al. obviously teaches that a patient can take an additional dosage as needed. (Final Office Action at page 18.)

Regarding the first sentence quoted above, Appellant fails to see how a statement in Kuna *et al.* (or even Rabe *et al.*, if that is what the Examiner meant to say)[3] that all treatments are "well tolerated" has anything to do with the issues here. "Well tolerated" simply means that the treatments did not cause undue discomfort or side effects—it says nothing at all about relative efficacy. The surprising results reported by Rabe *et al.* and relied upon here have to do with important measures of efficacy. And the second sentence in the passage quoted from the Final Office Action ("Thus, regardless if the rate of exacerbations were lowered, the Carling et al. method still treats asthma") is no more pertinent than the first. As noted in the discussion of Kuna *et al.* above, evidence of surprising results cannot be dismissed simply because the prior art method is also useful in treating asthma. Appellants have proven that the present method has very significant and surprising advantages over the prior art method. If properly taken into

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[3] Since the Kuna *et al.* abstract says nothing about whether the treatments were "well tolerated," Appellant presumes that the Examiner meant to refer to the Rabe *et al.* abstract.

account, that should be dispositive of nonobviousness, particularly in view of the teachings-away in the art described at length above.

Still other surprising results are reported in the publications enclosed as Exhibits 9 and 10. Exhibit 9 is Scicchitano *et al.*, "Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma," Curr Med Res Opin 20(9):1403-1418 (2004). Exhibit 10 is Bousquet *et al.*, "Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone," Resp Med 101:2437-2446 (2007). Each of these studies compared treatment in accordance with the present invention to other methods of treating asthma involving fixed doses of glucocorticosteroid, and found that the presently claimed methods were far superior in reducing the number of exacerbations, as well as by other measures of efficacy, ***even though the patients treated in accordance with the presently claimed methods received a much lower total dose of inhaled corticosteroid.***

In response, the Final Office Action argues at pages 18-19 that this evidence is not persuasive:

> Although, the adjustable maintenance dosing is more effective, Scicchitano et al. also teaches that both the fixed and adjustable dosing treatments were equally well tolerated....The Examiner would still like to point out that the Carling et al. method still <u>effectively</u> treats asthma, in which the claims are drawn toward. (Informal English in the original.)

As previously discussed, being "well tolerated" says nothing about efficacy and is pretty much irrelevant to the issues. Also irrelevant is the fact that "the Carling et al. method still effectively treats asthma," since Appellant has submitted the evidence to show surprisingly <u>better</u> results with the presently claimed methods in comparison with various prior art methods, and not in reliance on any allegation that the prior art methods don't work. See the arguments on these points in the discussions of Rabe *et al.* and Kuna *et al.* above.

It is noted that the Final Office Action provides no reason for dismissing the Bousquet *et al.* evidence.

Appellant submits that the Examiner has not put forward a single legitimate argument as to why the evidence of record disclosing surprising results does not overcome the *prima facie* obviousness rejection, particularly in view of the teachings-away in the art discussed above that would have led those of ordinary skill to expect (a) no benefit, and (b) a potentially serious risk

of harm. Nor has the Examiner provided any evidence to counter the surprising results evidence submitted by Appellant. Any one of the clinical studies submitted in this case (Exhibits 4 and 7-10) should have been dispositive as to nonobviousness. Taken together, the evidence is overwhelming.

Other Objective Indicia of Nonobviousness

At least as far back as the *Graham* case, the courts have recognized that so-called "objective indicia of nonobviousness" are potentially valuable indicators of how those of ordinary skill in the art would have viewed the claimed invention at the priority date. The evidence of record includes several statements that fall into various accepted categories of objective indicia of nonobviousness.

For example, the Barnes editorial discussed above (Exhibit 5) begins with the following statement of *long felt, unsatisfied need* for an effective asthma treatment: "**Despite the availability of highly effective therapies, many patients with asthma continue to suffer symptoms and exacerbations, with considerable disruption to their daily life.**" (Though Barnes does not use the term "long felt," it stands to reason that this was not a new problem.) Barnes, an expert in the field of asthma therapies who is associated with the National Heart and Lung Institute, Imperial College, London, UK, goes on to discuss O'Byrne *et al.*'s (Exhibit 4) findings that treatment with combination inhaler for both maintenance and relief "**markedly reduced the number of severe exacerbations…over the 1-year treatment period compared with the other treatments**", and also "**reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens,**" implying that here at last may be a way to satisfy that long felt need, at least for many patients inadequately served by prior therapies. Barnes offers his view that the O'Byrne *et al.* study "**may lead to changes in the paradigm of asthma management,**" another indication that he believe it is at least a partial answer to the long felt need. Barnes also describes what amounts to past *skepticism of experts* regarding the claimed method: "**A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid.**" He then reassures the reader: "**However, this was not the case, as the mean number of additional doses of combination**

inhaler was only one dose per day and very few patients used high doses." Finally, the editorial makes the point that the O'Byrne *et al.* findings were "**remarkable**" and "**surprisingly good results**," supporting quite literally Appellant's thesis that the present claimed methods produce *surprising results* compared to both the prior art Carling *et al.* method and the prior art budesonide-only method, results that could not have been predicted in view of any of this prior art.

The Scicchitano *et al.* article (Exhibit 9) discussed above also begins with a description of a *long-felt, unsatisfied need* in the art for a better treatment for asthma:

> **Despite the availability of international asthma guidelines and effective anti-inflammatory and bronchodilator medications, many patients continue to suffer from poorly controlled asthma. This is partly due to poor adherence to inhaled corticosteroid (ICS) therapy, as patients often over-rely on their short-acting β_2-agonist reliever medication in order to achieve rapid relief from symptoms, at the expense of their daily maintenance therapy.** (Page 1404, left column)

Schicchitano *et al.* conclude their article by suggesting that the presently claimed method may satisfy that long-felt need:

> **In conclusion, we have shown that a novel asthma management concept using budesonide/formoterol in a single inhaler for both maintenance therapy and relief from symptoms is a valid and beneficial strategy for the treatment of moderate to severe asthma – and could represent a potential advance in asthma treatment, both in terms of increased efficacy and a simplification of the treatment regimen.** (Page 1417, left column)

Likewise, the D'Urzo article (Exhibit 6) discussed above opens with a statement of *long-felt, unsatisfied need* for a more effective treatment for asthma:

> **Despite aggressive fixed-dose (FD) combination therapy with inhaled glucocorticosteroids (ICS) and long acting β_2-adrenoceptor agonists (LABA), many patients with asthma remain suboptimally controlled, based on the need for rescue therapy and rates of severe exacerbations.** (Abstract, page 385)

After a discussion of past efforts to solve the problem, the D'Urzo article at page 387, right column, describes the results of "**the recent landmark trial by O'Byrne [et al.]**" (i.e., the study reported in Exhibit 4) and says "**This finding suggests that it is (in part) the timing of the ICS dose in response to worsening asthma symptoms, rather than the total daily dose of ICS,**

that determines efficacy." D'Urzo refers to both the O'Byrne *et al.* (Exhibit 4) and the Scicchitano *et al.* (Exhibit 9) studies in saying that the presently claimed method helps satisfy the need in the art:

> **These studies underscore the potential to utilize a simple and practical asthma management approach that is associated with a high level of efficacy in patients with moderate-to-severe asthma. These studies also suggest that rescue therapy with budesonide/formoterol may be associated with more rapid stabilization of control during periods of asthma worsening.** Page 388, left column

D'Urzo concludes with effusive *praise* for the presently claimed method:

> **The concept of single-inhaler maintenance and reliever therapy represents one of the most important advances in asthma management in many years, and one that appears particularly well suited for utilization in the primary care setting.** (Page 390, right column)

The above statements by Barnes, Scicchitano *et al.*, and D'Urzo make clear their shared view that there was a *long-felt, unsatisfied need* in the art for an improved method of asthma treatment, and that use of a budesonide/formoterol combination inhaler for both maintenance and relief in accordance with the present invention helps satisfy that need for many patients. All three articles laud the benefits and singular importance of the new method. The Examiner has found all of this objective evidence to be unpersuasive, based on nothing more than her subjective interpretation of Carling *et al.* and her apparent view that one would obviously have selected the budesonide/formoterol combination for alleviating an acute attack, rather than a short-acting bronchodilator that is normally used for that purpose. To arrive at this conclusion, the Examiner has had to find various excuses (all improper) to dismiss all of Appellant's voluminous evidence of teachings-away, surprising results, and objective assessments by experts in the field. It is clear from the Exhibits and the arguments presented above that one of ordinary skill in the art of asthma therapy at the priority date would not have interpreted Carling *et al.* as suggesting that a budesonide-containing product such as the budesonide/formoterol combination product should be administered in accordance with the present claims. The paradigm for use of steroid-containing products dictated fixed dosage use for maintenance therapy, not variable dosage as determined day-to-day by the patient, e.g., for relief of an acute attack or when the

patient expect to encounter an asthma inducing condition. And certainly Carling *et al.* gave no reason to expect the surprisingly good results reported by O'Byrne *et al.*, Kuna *et al.,* Rabe *et al.,* Scicchitano *et al.,* and Bousquet *et al.,* and commented upon by Barnes and D'Urzo.

In view of the foregoing, the rejection of claims 13-15, 17, 18, 20-29, 34, 36, 42-50, and 52-55 as obvious in view of Carling *et al.* is unwarranted, and should be reversed.

B. Rejection of claims 16 and 19 under 35 USC § 103(a) as being unpatentable over Carling *et al.* in view of Aberg *et al.* and in further view of Ryrfeldt *et al.*

Claims 16 and 19 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (as applied to claims 13-15, 17, 18, 20-29, 34, 36, 42-50, and 52-55 above) in view of Aberg *et al.* (U.S. Patent 5,795,564; Exhibit 12) and Ryrfeldt *et al.* ("Pulmonary disposition of the potent glucocorticoid budesonide, evaluated in an isolated perfused rat lung model," *Biochem. Pharmacol.* 38:17-22, 1989; Exhibit 13). The Examiner stated at page 10 of the Final Office Action that "Carling *et al.* does teach the isomer of formoterol set forth in claim 16 and the specified epimer of budesonide set forth in claim 19." Appellant finds no such teaching in Carling *et al.* Since the Examiner did not respond to Appellant's request (in the Amendment filed July 27, 2007) to point out where in Carling *et al.* the Examiner found those teachings, Appellant assumes that this statement was originally made in error and simply reproduced in every Office action since that date. Given the context of the rejection as a whole (i.e., the citation of secondary references Aberg *et al.* and Ryrfeldt *et al.*), it is likely the Examiner meant to say the inverse: *i.e.*, "Carling *et al.* does not teach…"

The Final Office Action also stated at pages 10-11 that

> Aberg et al. teaches (R,R) isomer of formoterol as required by claim 16 is a potent bronchodilator with reduced adverse effects in treatment of asthma…Ryrfeldt et al. teaches that the 22R epimer of budesonide is more potent in the treatment of bronchial asthma than 22S epimer…To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of Carling et al. and the (R,R) enantiomer of formoterol and the 22R epimer of budesonide because Aberg et al. and Ryrfeldt et al. teach that these specific isomers possess potent asthmatic effect. The motivation employ the (R,R) isomer of formoterol and 22R epimer of budesonide in the Carling et al. composition is because there is a reasonable expectation of successfully treating asthmatic patients with a

more effective medication with reduced adverse effects. (Non-standard English in the original)

Claims 16 and 19, which depend from claim 13, are patentable for at least the reasons discussed above with respect to claim 13 and the rest of the independent claims. The teachings of Aberg *et al.* and Ryrfeldt *et al.* do not make up for Carling *et al.*'s deficiencies as outlined above, and indeed are cited solely for their teachings concerning specific epimers of the active ingredients. Accordingly, Appellant requests that the rejection of claims 16 and 19 under § 103(a) be reversed.

C. Rejection of claims 57-66 under 35 USC § 103(a) as being unpatentable over Carling *et al.* in view of Trofast (U.S. Patent No. 5,983,956).

Claims 57-66 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (as applied to claims 13-15, 17, 18, 20-29, 34, 36, 42-50, and 52-55 above) in view of Trofast (U.S. Patent No. 5,983,956; Exhibit 14; "Trofast"). The Final Office Action states at page 11 that "Carling *et al.* does teach the specific amount of 4.5 μg of formoterol fumarate dihydrate or the specific amounts of budesonide in claims 57-68." Appellant finds no such teaching in Carling *et al.*, and supposes the Examiner may have meant to say the inverse: *i.e.*, "Carling *et al.* does not teach…"

The Final Office Action cites Trofast as allegedly teaching that formoterol fumarate dihydrate can be administered via inhalation from 3 to 24 μg in doses of 3, 4.5, 6, 9 or 12 μg. The Examiner does not explain where she believes the prior art discloses the particular amounts of budesonide variously specified in claims 57-68; perhaps the generic discussion on page 12 of the Final Office Action regarding obviousness that "typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art" was meant to substitute for finding a disclosure in the art regarding the precise amounts of budesonide specified in claims 57-66 as being delivered in each puff from the inhaler. The discussion in the Final Office Action is so generic that it is difficult to tell what was intended. However, this issue is largely moot because claims 57-66, which variously depend from independent claims 13, 36, 42, 49, and 50, are patentable for at least the reasons discussed above with respect to the independent claims. Trofast plainly does not make up for Carling *et al.*'s deficiencies as outlined above, and indeed

appears to have been cited solely for its teachings concerning the size of the dose of formoterol fumarate dihydrate. Accordingly, Appellant requests that the rejection of claims 57-66 under § 103(a) be reversed.

D. Provisional rejection of claims 13-15, 17, 19, 20, 22-25, 34, 36, 42, 53 and 57-66 for nonstatutory obviousness-type double patenting over claims 13-15, 17, 19, 20, 22-25, 30-36, 38, and 42 of U.S. Application No. 09/367,950.

The Final Office Action provisionally rejects claims 13-15, 17, 19, 20, 22-25, 34, 36, 42, 53 and 57-66 for nonstatutory obviousness-type double patenting over claims 13-15, 17, 19, 20, 22-25, 30-36, 38, and 42 of U.S. Application No. 09/367,950 (the '950 Application), the parent of the present application. The '950 Application became abandoned by failure to reply to an Office action mailed December 15, 2010. See the Notice of Abandonment mailed in the '950 Application by Examiner Jennifer Kim on June 21, 2011. As the '950 Application is no longer pending, the double patenting rejection over the claims of the '950 Application is moot. Reversal of the rejection is respectfully requested.

CONCLUSION

For the reasons set forth above, Appellant respectfully requests that the rejections of claims 13-29, 34, 36, 42-50, 52-55, and 57-66 be reversed.

The attached Claims Appendix (viii) contains a copy of the claims under appeal.

The attached Evidence Appendix (ix) lists Exhibits 1-14. The Exhibits are being filed along with this Brief on Appeal.

The attached Related Proceedings Appendix (x) includes a copy of the Board's decision in Appeal 2007-1154.

The appeal brief fee of $540 required by 37 C.F.R. § 41.20(b)(2) is being paid via the Electronic Filing System. The fee for a five-month extension of time (to August 10, 2011) was paid when the Supplemental Amendment was filed on July 29, 2011. Please apply any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-188002.

Respectfully submitted,

Date: August 2, 2011

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(viii) Claims Appendix

1.-12. (Canceled)

13. A method of treating asthma in a patient, the method comprising administering an effective amount of a composition comprising, in admixture:

(a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient that is budesonide;

characterized in that the patient is administered (i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses on an irregular basis, wherein the one or more additional doses are administered as-needed, as determined by the patient.

14. The method according to claim 13, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:100.

15. The method according to claim 13, wherein the first active ingredient is formoterol fumarate dihydrate.

16. The method according to claim 13, wherein the first active ingredient is the R,R enantiomer of formoterol or a pharmaceutically acceptable salt or solvate of said enantiomer or a solvate of such a salt.

17. The method according to claim 15, wherein the composition is in the form of unit doses, each of which delivers 1 μg to 48 μg of the first active ingredient, calculated as formoterol fumarate dihydrate.

18. The method according to claim 15, wherein the patient is administered an amount per day of the composition, including for maintenance therapy, that contains a total of 1 μg to 100 μg of the first active ingredient, calculated as formoterol fumarate dihydrate.

19. The method according to claim 13, wherein the second active ingredient is the 22R epimer of budesonide.

20. The method according to claim 13, wherein the composition is in the form of unit doses, each of which delivers 20 μg to 1600 μg of budesonide to the patient.

21. The method according to claim 13, wherein the patient is administered an amount per day of the composition, including for maintenance therapy, that contains a total of 20 μg to 4800 μg of budesonide.

22. The method according to claim 13, wherein the particle size of the active ingredients (a) and (b) is less than 10 μm.

23. The method according to claim 13, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

24. The method according to claim 13, wherein the composition additionally comprises lactose monohydrate.

25. The method according to claim 14, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:70.

26. The method according to claim 17, wherein the composition is in the form of unit doses, each of which delivers 3 μg to 12 μg of the first active ingredient to the patient, calculated as formoterol fumarate dihydrate.

27. The method according to claim 18, wherein the patient is administered an amount per day of the composition, including maintenance therapy, that contains a total of 2 μg to 60 μg of the first active ingredient, calculated as formoterol fumarate dihydrate.

28. The method according to claim 20, wherein the composition is in the form of unit doses, each of which delivers 50 μg to 400 μg of budesonide to the patient.

29. The method according to claim 21, wherein the patient is administered an amount per day of the composition, including maintenance therapy, that contains a total of 30 μg to 3200 μg of budesonide.

30-33. (Canceled)

34. The method of claim 36 wherein the asthma inducing condition is selected from the group consisting of exercise, exposure to cold air, exposure to pollen, exposure to perfume, and exposure to a smoky environment.

35. (Canceled)

36. A method of treating asthma in a patient, the method comprising

administering an effective amount of a composition comprising, in admixture:

(a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient that is budesonide;

characterized in that the patient is administered (i) a maintenance dose of the composition twice per day on a regular basis, and (ii) one or more additional doses on an irregular basis, wherein the one or more additional doses are administered when the patient expects to encounter an asthma inducing condition.

37-41. (Canceled)

42. A method of treating asthma in a patient, the method comprising

administering an effective amount of a composition comprising, in admixture:

(a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient that is budesonide;

characterized in that the patient is administered (i) a maintenance dose of the composition twice per day on a regular basis, and (ii) one or more additional doses, wherein the one or more additional doses are administered when the patient experiences an acute asthma attack.

43. The method of claim 13, wherein the first and second active ingredients are both in dry powder form.

44. The method of claim 13, wherein the composition is administered from a pressurized metered dose inhaler.

45. The method of claim 44, wherein the first and second active ingredients are suspended in a liquid propellant.

46. The method of claim 45, wherein the liquid propellant is one or more of P134a, P152a, and P227.

47. The method of claim 45, wherein the liquid propellant is P227.

48. The method of claim 13, wherein the composition is administered by the patient.

49. A method of treating asthma in a patient, the method comprising administering an effective amount of a composition comprising, in admixture:

(a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient that is budesonide;

characterized in that the patient is administered (i) a maintenance dose of the composition twice per day on a regular basis, and (ii) one or more additional doses on an irregular basis, wherein the one or more additional doses are administered when needed for symptom relief.

50. A method of treating asthma in a patient, the method comprising administering an effective amount of a composition comprising, in admixture:

(a) a first active ingredient that is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient that is budesonide;

characterized in that the patient is administered (i) a maintenance dose of the composition on a regular basis as determined by the patient's physician, and (ii) one or more additional doses on an irregular basis, wherein the one or more additional doses are administered when the patient determines the additional dose or doses are needed for symptom relief or when the patient expects to encounter an asthma inducing condition.

51. (Canceled)

52. The method of claim 36, wherein the first active ingredient is formoterol fumarate dihydrate.

53. The method of claim 42, wherein the first active ingredient is formoterol fumarate dihydrate.

54. The method of claim 49, wherein the first active ingredient is formoterol fumarate dihydrate.

55. The method of claim 50, wherein the first active ingredient is formoterol fumarate dihydrate.

56. (Canceled)

57. The method of claim 13, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient.

58. The method of claim 13, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient.

59. The method of claim 36, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient.

60. The method of claim 36, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient.

61. The method of claim 42, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient.

62. The method of claim 42, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient.

63. The method of claim 49, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient.

64. The method of claim 49, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient.

65. The method of claim 50, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 80 μg budesonide to the patient.

66. The method of claim 50, wherein the composition is inhaled by the patient from an inhaler, and each puff from the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 160 μg budesonide to the patient.

67-68. (Canceled)

(ix) Evidence Appendix

These Exhibits 1-14 are being uploaded onto EFS separately from the Brief on Appeal, but within the same transmission.

Exhibit 1: Product insert, Pulmicort® Turbuhaler® budesonide inhaler product (1997)

Exhibit 2: Product insert, Symbicort® Turbuhaler® budesonide/formoterol inhaler product (2001)

Exhibit 3: Patient's Instructions for Use, Advair Diskus® fluticasone propionate/salmeterol xinafoate inhaler product (March 2003)

Exhibit 4: O'Byrne *et al.,* "Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma," *Am J Respir Crit Care Med* 171:129-136, 2005

Exhibit 5: Barnes, "A Single Inhaler for Asthma?" *Am J Respir Crit Care Med* 171:95-96, 2005

Exhibit 6: D'Urzo, "Inhaled Glucocorticosteroid and Long-Acting β2-Adrenoceptor Agonist Single-Inhaler Combination for Both Maintenance and Rescue Therapy: A Paradigm Shift in Asthma Management" *Treat Respir Med* 5:385-391 (2006)

Exhibit 7: Kuna *et al.*, "Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations," *Int J Clin Pract* 61:725-736 (2007)

Exhibit 8: Rabe *et al.*, Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study," *Lance*t 368:744-753 (2006)

Exhibit 9: Scicchitano *et al.*, "Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma," *Curr Med Res Opin 20(9):*1403-1418 (2004)

Exhibit 10: Bousquet *et al.*, "Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone," *Resp Med* 101:2437-2446 (2007)

Exhibit 11: Carling *et al.,* WO 93/11773

Exhibit 12: Aberg *et al.,* U.S. Patent No. 5,795,564

Exhibit 13: Ryrfeldt *et al.*, "Pulmonary disposition of the potent glucocorticoid budesonide, evaluated in an isolated perfused rat lung model," *Biochem Pharmacol* 38:17-22, 1989

Exhibit 14: Trofast, U.S. Patent 5,983,956

(x) Related Proceedings Appendix

The decision of the Board of Patent Appeals and Interferences in Appeal 2007-1154 dated August 28, 2007, is attached. That Appeal was in a co-pending related case, U.S. Serial No. 09/367,950.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte TOMMY EKSTROM

Appeal 2007-1154
Application 09/367,950
Technology Center 1600

Decided: August 28, 2007

Before TONI R. SCHEINER, DONALD E. ADAMS, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

ORDER REMANDING TO THE EXAMINER

This appeal under 35 U.S.C. § 134 involves claims 13-36, 38, 42, and 43, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

INTRODUCTION

The claims are directed to a method of prevention and treatment of asthma symptoms. Claim 13[1] is illustrative:

13. A method of prevention and treatment of asthma symptoms, which comprises

instructing a patient in need thereof to inhale an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms.

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[1] In response to a Notice of Non-Compliant Appeal Brief (mailed October 30, 2006), Appellant filed amended claims to replace "all prior versions and listings of claims in the application" (Amendment in Reply to Non-Compliant Appeal Brief, received January 18, 2007 2). On January 24, 2007, the Examiner entered the amendment in an Office communication (Office communication 2 (since this document was not paginated, page 2 refers to the second page of the document assuming it was paginated beginning with the cover page as page 1). Accordingly, the claims before us on appeal are as they appear in Appellant's Amendment in Reply to Non-Compliant Appeal Brief, received January 18, 2007.

The Examiner relies on the following prior art references to show unpatentability:

Carling	WO 93/11773	June 24, 1993
Aberg	US 5,795,564	Aug. 18, 1998

Ryrfeldt, "PULMONARY DISPOSITION OF THE POTENT GLUCOCORTICOID BUDESONIDE, EVALUATED IN AN ISOLATED PERFUSED RAT LUNG MODEL," *Biochemical Pharmacology*, Vol. 38, No. 1, pp. 17-22 (1989).

The rejections as presented by the Examiner are as follows:

1. Claims 13, 35, 36, and 42 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

2. Claims 13-15, 17, 18, 20-36, 38, 42, and 43 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Carling.

3. Claims 16 and 19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Carling, Aberg, and Ryrfeldt.

We reverse the rejection under the enablement provision of 35 U.S.C. § 112, first paragraph. We find, however, that the rejections under 35 U.S.C. § 103(a) are not in condition for a decision on appeal. For the reasons that follow remand the application to the Examiner to consider the following issues and to take appropriate action.

DISCUSSION

Enablement:

Claims 13, 35, 36, and 42 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

The Examiner finds that Appellant's Specification does not provide an enabling disclosure "for the 'prevention of an acute episode of asthma'"

(Answer 3). The Examiner finds that "[t]he claims encompass prevention of a complex cell[ular] autoimmune disorder in humans which has potentially many different causes (i.e. many different allergen[s] or combination[s] of allergens). Each of which may or may not be addressed by the administration of the claimed composition" (Answer 4-5). According to the Examiner, the prevention of an acute episode of asthma in a human with the claimed compounds is unpredictable, "the state of the art with regard to *prevention* of . . . [acute asthmatic attack] is underdeveloped[,]" and the working examples provided in Appellant's Specification do not address the "prevention of an acute episode of asthma" (Answer 5). Based on this reasoning, the Examiner concludes that "it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of an acute episode of asthma in a subject by administration of the claimed composition" (Answer 6).

In response, Appellant asserts that the prevention of acute episodes of asthma is disclosed in the [S]pecification at page 3, lines 7-19,

> Acute asthma attacks may occur on an irregular basis when exposed to an agent e.g., during the pollen season, a virus infection, cold air, perfumes or any other agent(s) triggering an asthma attack in the patient . . . We contemplate preventive use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions.

This "preventive use" is accomplished by simply using the formoterol/budesonide composition that is taught throughout the [S]pecification (the same composition as for treatment), delivered via inhalation in the manner that is taught throughout the [S]pecification (the same delivery method as for treatment), but where the timing of the administration is at a point before

> the symptoms of an acute attack begin, or early in the development of an acute attack when the symptoms are still relatively minor but are felt by the patient. When a patient knows in advance that he/she is about to encounter asthma-triggering conditions such as those mentioned in the [S]pecification, he/she can take preventative action by using the formoterol/budesonide inhaler in accordance with the claimed methods, i.e., "on demand" or "as needed."

(Br. 5.)

We find that Appellant has the better argument and the rejection is reversed.

Obviousness:

Claims 13-15, 17, 18, 20-36, 38, 42, and 43 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Carling; and Claims 16 and 19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Carling, Aberg, and Ryrfeldt. Claims 16 and 19 depend from claim 13, accordingly, to simplify our discussion, we will focus on representative claim 13.

Claim 13 is drawn to a method of prevention and treatment of asthma symptoms. The method comprises the single step of instructing a patient in need thereof to inhale an effective amount of a composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms.

In addition, claim 13 defines the composition as comprising in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide.

Written descriptive support:

As an initial matter, we note that Appellant's Specification discloses the step of administering an effective amount of the composition set forth in claim 13 to a patient in need thereof (*see*, *e.g.*, Specification 3: 21-27), but the Specification, including the originally filed claims, does not appear to contain a literal disclosure of a method wherein a patient is instructed to inhale an effective amount of a composition on demand. "Although the exact terms need not be used in haec verba, . . . the [S]pecification must contain an equivalent description of the claimed subject matter" (*Lockwood v. American Airlines Inc.*, 107 F.3d 1565, 1571-1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)).

The phrases "instructing a patient to inhale" and "instructing a patient to inhale the composition on demand" were added to the claim in Appellant's April 20, 2001 Response to the Examiner's December 18, 2000 Non-final Action (Response 1-3). Accordingly, we remand the application to the Examiner to clarify where written descriptive support for the foregoing phrases is found in Appellant's Specification. In this regard, we encourage Appellant to be an active participant in this determination and clearly explain where written descriptive support for this added language is found in their Specification.

Claim interpretation:

In the event that Appellant's Specification provides adequate written descriptive support for the phrases "instructing a patient to inhale" and "instructing a patient to inhale the composition on demand," the Examiner should take this opportunity to explain how these phrases are to be interpreted; and how the relevant prior art relates to this claim interpretation.

Claim 13 is drawn to a method of (1) treating and (2) preventing asthma symptoms. As discussed below, the treatment of asthma symptoms with a twice daily administration of the composition of claim 13 was known in the art. While the single step in claim 13 requires that a patient be instructed to inhale a composition on demand, it appears that there is nothing in claim 13 that requires that a patient actually inhale the composition; or if inhaled, that the patient inhale the composition more than is recognized in the art.

Stated differently, claim 13 only requires that the patient be instructed to do something (e.g., inhale a composition) on demand when the patient experiences an increase in asthma symptoms. There is no requirement that the patient actually inhale the composition (Oral Hearing Transcript 7: 11-19). According to Appellant the "prevention" of asthma symptoms is accomplished by administering the same composition as is used for treating

> but where the timing of the administration is at a point before the symptoms of an acute attack begin, or early in the development of an acute attack when the symptoms are still relatively minor but are felt by the patient. When a patient knows in advance that he/she is about to encounter asthma-triggering conditions such as those mentioned in the [S]pecification, he/she *can* take preventative action by using the formoterol/budesonide inhaler in accordance with the claimed methods, i.e., "on demand" or "as needed."

(Br. 5, emphasis added.) We emphasis Appellant's use of the word "can," because while claim 13 requires that a patient be instructed to take the composition on demand, the patient may elect to take the composition for maintenance therapy (e.g., twice a day), twice a day only during the allergy season when asthma symptoms flair up, every five minutes, more often, or not at all.

In this regard, it may be that inhalation "on demand" reads on a range of circumstances wherein patients will never inhale the composition (e.g., the lower limit of 0 inhalations), or will inhale the composition an undefined number of times (e.g., an undefined upper limit). It would appear that those patients who will inhale the composition conventionally, e.g., two-times per day to prevent and treat asthma symptoms, would be included in this range (*see infra*).

This interpretation would appear to be consistent with the manner in which Appellant's representative interpreted claim 13 at the May 17, 2007 Oral Hearing. Specifically, Appellant's representative stated that claim 13 "specifies just the on-demand part, which could mean zero times a day . . . [or] [i]t could end up being no more than two times a day" (Oral Hearing Transcript 4: 3-8.).

As the Examiner explains (Answer 7), Carling teaches a composition comprising formoterol and budesonide, the first and second active ingredients of Appellant's composition (Carling 4: 23-28). Carling's composition is "for administration by inhalation in the treatment of respiratory disorder . . ." (Carling 4: 30-34). According to Carling, "[t]he intended dose regimen is a twice daily administration" (Carling 6: 22-23).

Carling teaches that the combination of formoterol and budesonide "permits a twice daily dosing regime as a basic treatment of asthma. . ." (Carling 4: 20-21).

Appellant does not dispute that Carling teaches a composition within the scope of claim 13 or that Carling teaches the administration of this composition by inhalation twice a day to treat and prevent asthma symptoms (Br. 14-15). Instead, Appellant contends that Carling differs from the claimed invention, by not teaching the administration of the composition on demand (Br. 17). According to Appellant,

> a person having ordinary skill in the art of asthma therapy would not have been motivated [by Carling] to instruct a patient to inhale a composition comprising both budesonide and formoterol more than twice daily, or to instruct a patient to inhale the composition on demand, or as needed, such that the therapy would be administered more than twice daily.

(Reply Br. 9.) However, as discussed above, Appellant admits that the term "on demand" reads on the administration of the composition to a patient zero times per day or twice a day. Therefore, Carling would appear to teach the administration of the same composition, to the same patient population (patients suffering from asthma symptoms), and in the same dosage (twice a day) as is encompassed by Appellant's interpretation of claim 13.

The question remains, however, whether Carling's disclosure can be reasonably interpreted to read on the "on demand" requirement in Appellants' claims. Therefore, the Examiner should make express findings of how the phrase "instructing a patient to inhale the composition on demand" is to be interpreted.

Statutory subject matter:

The Examiner should also take this opportunity to clearly explain whether the claim constitutes a statutory process. Claim 13 requires only one positive step – instruct a patient to inhale a composition on demand. According to Appellant what happens after the patient is instructed to inhale the composition is not an element of the claim (Oral Hearing Transcript 11: 4-8). According to Appellant this step can be performed by any number of routes, including printed matter (e.g., a product insert accompanying an inhaler) (Oral Hearing Transcript 2: 21-24). Stated differently, this claim appears to be directed to the manipulation of an abstract idea (e.g., the communication of a concept) without any requirement that a practical application actually be associated with this abstract idea. In this regard, we note that "[a] process is . . . an act, or a series of acts, *performed upon the subject matter to be transformed and reduced to a different state or thing.*" *In re Schrader*, 22 F.3d 290, 293-94, 30 USPQ2d 1455, 1459 (Fed. Cir. 1994), citation omitted. (*See* also *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F3d 1368, 1373, 47 USPQ2d 1596, 1601 (Fed. Cir. 1998) holding that a claimed system was statutory subject matter because it produced "a useful, concrete and tangible result.")

Accordingly, we remand the application to the Examiner to clearly explain what subject matter the claimed process is transforming or reducing into a different state or thing.

CONCLUSION

In summary, we reverse the rejection under enablement provision of 35 U.S.C. § 112, first paragraph and remand the application for further

consideration. Any further communication from the examiner which contains a rejection of the claims should provide appellants with a full and fair opportunity to respond. In addition, as set forth above, Appellant should take an active role in clarifying the foregoing issues.

REVERSED and REMANDED

Ssc

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